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accessing the remaining file names entered.
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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.22       0.22

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=> s fusion protein
L1      270850 FUSION PROTEIN

=> s l1 and DAF
L2         299 L1 AND DAF

=> s l2 and IgG4
L3           3 L2 AND IGG4
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L4 3 DUP REMOVE L3 (0 DUPLICATES REMOVED)

=> d l4 1-3 cbib abs

L4 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2007:350058 Document No. 146:378219 Transgenic ungulates, such as pigs, expressing CTLA4-Ig and uses thereof in xenotransplantation. Ayares, David Lee; Cooper, David K. C. (Revivicor, Inc., USA). PCT Int. Appl. WO 2007035213 A2 20070329, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US30842 20060809. PRIORITY: US 2005-706843P 20050809.
AB The present invention provides ungulates, including pigs, expressing CTLA4-Ig, as well as tissue, organs, cells and cell lines derived from such animals. Such animals, tissues, organs and cells can be used in research and medical therapy, including xenotransplantation. In addition, methods are provided to prepare organs, tissues and cells expressing the CTLA4-Ig for use in xenotransplantation, and nucleic acid constructs and vectors useful therein.

L4 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2006:100311 Document No. 144:184670 RAGE-Ig **fusion proteins** and therapeutic uses thereof. O'Keefe, Theresa; Luciano, Peter; Qin, Shixin (Critical Therapeutics, Inc., USA). PCT Int. Appl. WO 2006012415 A2 20060202, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US25877 20050720. PRIORITY: US 2004-589678P 20040720.
AB The present invention is drawn to **fusion proteins** comprising a Receptor for Advanced Glycation Endproducts (RAGE) and an Ig element. In some embodiments the **fusion protein** may also be bound to RAGE ligand or its RAGE-binding fragment, such as HMGB1 A box. The invention also encompasses methods of treating a condition characterized by activation of an inflammatory cytokine cascade comprising administering such **fusion proteins**. The invention is also drawn to nucleic acids encoding the **fusion proteins**, as well as vectors and cells comprising such nucleic acids. Provided are protein and cDNA sequences for RAGE-Ig **fusion proteins**.

L4 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:696571 Document No. 143:171338 Chimeric proteins comprising complement control protein repeats of **DAF**, CR1 and/or MCP, **IgG4** polypeptide and lipid tail for regulating complement activation. Medof, Edward; Kuttner-Kondo, Lisa (Case Western Reserve University, USA). PCT Int. Appl. WO 2005069726 A2 20050804, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU,

ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB50257 20050121. PRIORITY: US 2004-537860P 20040121.

AB A hybrid complement-regulating protein comprises a first functional unit of a first complement regulatory protein having complement regulating properties, a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties and at least a second functional unit attached to the spacer sequence. The second functional unit may be a polypeptide providing a functional unit of a second complement regulatory protein, a polypeptide derived from an Ig, or a polypeptide that enhances binding of the protein to an animal cell. The hybrid protein may also contain a second spacer sequence and a third functional unit of a complement regulatory protein, a polypeptide derived from an Ig, and a polypeptide that enhances binding of the protein to an animal cell. The optional third functional unit may be the same or different from the first or second functional units. The functional units of complement regulatory protein are complement control protein repeats (CCPs) of decay-accelerating factor (**DAF**), complement receptor 1 (CR1) and membrane cofactor protein (MCP). The chimeric proteins are particularly useful for inhibiting excessive complement activation and for treating diseases such as reperfusion injury, stroke, septic shock, acute myocardial infarction, autoimmune disease, inflammatory bowel disease, etc.

=> s l2 and CD55
L5 65 L2 AND CD55

=> s l5 and Fc
L6 14 L5 AND FC

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PROCESSING COMPLETED FOR L6
L7 5 DUP REMOVE L6 (9 DUPLICATES REMOVED)

=> d l7 1-5 cbib abs

L7 ANSWER 1 OF 5 SCISEARCH COPYRIGHT (c) 2010 The Thomson Corporation on STN

2006:809155 The Genuine Article (R) Number: 075KM. Virus receptor trap neutralizes coxsackievirus in experimental murine viral myocarditis. Jeon E S (Reprint). Sungkyunkwan Univ, Sch Med, Dept Med, Cardiac & Vasc Ctr, Samsung Med Ctr, 50 Ilwon Dong, Seoul 135710, South Korea (Reprint). Lim B K; Choi J H; Nam J H; Gil C O; Shin J O; Yun S H; Kim D K. Sungkyunkwan Univ, Sch Med, Dept Med, Cardiac & Vasc Ctr, Samsung Med Ctr, Seoul 135710, South Korea; Catholic Univ Korea, Div Biosci & Technol, Puchon, South Korea. E-mail: esjeon@smc.samsung.co.kr. CARDIOVASCULAR RESEARCH (1 AUG 2006) Vol. 71, No. 3, pp. 517-526. ISSN: 0008-6363. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: The coxsackie and adenovirus receptor (CAR) and the decay-accelerating factor (**DAF**) are receptors for coxsackievirus B3 (CVB3), which is known as the major cause of human viral myocarditis. We investigated the potential for therapeutic use of soluble virus receptor **fusion proteins.**

Methods: We designed and generated a novel virus receptor trap (hCAR-hDAF:**Fc**) consisting of both CVB3 receptors and the

Fc portion of human IgG, and evaluated its antiviral effects in experimental CVB3 myocarditis.

Results: Among four soluble virus receptor **fusion proteins** (hCAR:**Fc**, hDAF:**Fc**, hCAR-hDAF:**Fc** and hDAF-hCAR:**Fc**), hCAR:**Fc** and hCAR-hDAF:**Fc** in the supernatant of transfected cells neutralized echovirus, adenovirus, and various serotypes of CVB in a dose-dependent manner. Both soluble viral receptor proteins bound to the VP0 and VP1 capsid proteins of CVB3. The in vivo efficacy of viral receptor proteins was evaluated by intramuscular injection of plasmid (hCAR:**Fc** or hCAR-hDAF:**Fc**) followed by electroporation in a murine model of CVB3 myocarditis. Serum levels of the virus receptor proteins increased relative to baseline values from day 3 and peaked on day 14 at 12.9-fold for hCAR:**Fc** and 7.1-fold for hCAR-hDAF:**Fc**. The 3-week survival rate was significantly higher in hCAR-hDAF:**Fc**-treated mice (61%) than in hCAR:**Fc**-treated mice (29%) and in controls (15%; $p < 0.05$). Myocardial inflammation, fibrosis, and myocardial virus titers were all significantly reduced in the hCAR:**Fc** and hCAR-hDAF:**Fc** groups compared to the controls.

Conclusion: Our soluble virus receptor trap, hCAR-hDAF:**Fc**, attenuated viral infection, myocardial inflammation, and fibrosis, resulting in higher survival rates in mice with coxsackieviral myocarditis. Furthermore, it consists exclusively of human components, and we demonstrated that this soluble virus receptor trap may be used as a potential candidate for a novel therapeutic agent for the treatment of acute viral myocarditis during the viremic phase.

L7 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 1

2004178777. PubMed ID: 15073680. Soluble recombinant coxsackievirus and adenovirus receptor abrogates coxsackievirus b3-mediated pancreatitis and myocarditis in mice. Yanagawa Bobby; Spiller O Brad; Proctor David G; Choy Jonathan; Luo Honglin; Zhang Huifang M; Suarez Agripina; Yang Decheng; McManus Bruce M. (The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Department of Pathology and Laboratory Medicine, St. Paul's Hospital/Providence Health Care-UBC, Vancouver, Canada.) The Journal of infectious diseases, (2004 Apr 15) Vol. 189, No. 8, pp. 1431-9. Electronic Publication: 2004-04-05. Journal code: 0413675. ISSN: 0022-1899. L-ISSN: 0022-1899. Pub. country: United States. Language: English.

AB BACKGROUND: Group B coxsackievirus infection can result in organ injury and inflammation. The coxsackievirus and adenovirus receptor (CAR) and decay-accelerating factor (**DAF; CD55**) have both been identified as receptors for coxsackievirus B3 (CVB3). We have shown elsewhere that early **DAF-Fc** treatment attenuates CVB3-induced myocarditis and virus replication. METHODS: CAR was synthesized as a soluble IgG1-**Fc fusion protein** (CAR-**Fc**). In vitro, CAR-**Fc** blocked infection by 2 different strains of CVB3. A/J mice were infected in vivo with CVB3 and were administered CAR-**Fc** either 3 days before infection, during infection, or 3 days after infection and were compared with mice infected with virus alone and control animals. RESULTS: All CAR-**Fc** treatment groups had reduced recoverable infectious virus in the heart. CAR-**Fc** treatment of mice, either preceding or concurrent with CVB3 infection, resulted in complete inhibition of myocardial lesion area, cell death and inflammation, and viral RNA. Early treatment also completely blocked inflammation and cell death in the pancreas, an organ that is normally very sensitive to infection. CONCLUSION: To our knowledge, CAR-**Fc** is the only protein that has been shown to block coxsackievirus infection of the pancreas. However, regardless of the efficacy of the test protein, target tissue cannot be rescued after day 3 of infection in the A/J mouse model.

L7 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 2

2003027130. PubMed ID: 12533688. Coxsackievirus B3-associated myocardial pathology and viral load reduced by recombinant soluble human decay-accelerating factor in mice. Yanagawa Bobby; Spiller O Brad; Choy Jonathan; Luo Honglin; Cheung Paul; Zhang Huifang M; Goodfellow Ian G; Evans David J; Suarez Agripina; Yang Decheng; McManus Bruce M. (UBC McDonald Research Laboratories/The iCAPTUR E Centre, Department of Pathology and Laboratory Medicine, St. Paul's Hospital/Providence Health Care-University of British Columbia, Vancouver British Columbia, Canada.) Laboratory investigation; a journal of technical methods and pathology, (2003 Jan) Vol. 83, No. 1, pp. 75-85. Journal code: 0376617. ISSN: 0023-6837. L-ISSN: 0023-6837. Pub. country: United States. Language: English.

AB Coxsackievirus B3 (CVB3) infection can result in myocarditis, which in turn may lead to a protracted immune response and subsequent dilated cardiomyopathy. Human decay-accelerating factor (**DAF**), a binding receptor for CVB3, was synthesized as a soluble IgG1-**Fc fusion protein** (**DAF-Fc**). In vitro, **DAF-Fc** was able to inhibit complement activity and block infection by CVB3, although blockade of infection varied widely among strains of CVB3. To determine the effects of **DAF-Fc** in vivo, 40 adolescent A/J mice were infected with a myopathic strain of CVB3 and given **DAF-Fc** treatment 3 days before infection, during infection, or 3 days after infection; the mice were compared with virus alone and sham-infected animals. Sections of heart, spleen, kidney, pancreas, and liver were stained with hematoxylin and eosin and submitted to in situ hybridization for both positive-strand and negative-strand viral RNA to determine the extent of myocarditis and viral infection, respectively. Salient histopathologic features, including myocardial lesion area, cell death, calcification and inflammatory cell infiltration, pancreatitis, and hepatitis were scored without knowledge of the experimental groups. **DAF-Fc** treatment of mice either preceding or concurrent with CVB3 infection resulted in a significant decrease in myocardial lesion area and cell death and a reduction in the presence of viral RNA. All **DAF-Fc** treatment groups had reduced infectious CVB3 recoverable from the heart after infection. **DAF-Fc** may be a novel therapeutic agent for active myocarditis and acute dilated cardiomyopathy if given early in the infectious period, although more studies are needed to determine its mechanism and efficacy.

L7 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 3

2002457176. PubMed ID: 12215393. Efficient generation of monoclonal antibodies for specific protein domains using recombinant immunoglobulin **fusion proteins**: pitfalls and solutions. Harris Claire L; Lublin Douglas M; Morgan B Paul. (Department of Medical Biochemistry, University of Wales College of Medicine, Tenovus Building, Heath Park, Cardiff, CF14 4XX, UK.. HarrisCL@cardiff.ac.uk) . Journal of immunological methods, (2002 Oct 15) Vol. 268, No. 2, pp. 245-58. Journal code: 1305440. ISSN: 0022-1759. L-ISSN: 0022-1759. Pub. country: Netherlands. Language: English.

AB Monoclonal antibody production (mAb) first requires the availability of large amounts of pure immunogen for animal immunisation and fusion screening procedures. To overcome this obstacle, we have developed a simple method for rapid generation of pure antigen by generation of recombinant protein containing the antigen of interest fused to the hinge and **Fc** domains of human immunoglobulin (Ig). The **Fc** domain forms a convenient 'tag' to enable detection of the protein in supernatant of transfected cells and for purification of immunogen by protein A affinity chromatography. The only requirement for immunogen preparation using this methodology is that a DNA sequence encoding a

portion of the molecule of interest is known and that a suitable PCR template is available. Antibody production can be tailored to specific protein domains, for example functional domains, by expressing solely those domains in the **fusion protein.** We illustrate the technique with two different fusions used to raise antibodies against the porcine and human analogues of a complement (C) regulatory protein, decay accelerating factor **(DAF) (CD55).** Use of the specific Ig-**fusion protein** and a control protein facilitated screening of fusions by ELISA. We demonstrate two expression systems used to generate Ig **fusion proteins**, the first utilised a commercial vector to incorporate an amino terminal leader sequence and carboxy terminal Ig domains. Low levels of expression required subcloning into a high expression vector and resulted in yields of **fusion protein** at between 2 and 10 mg per litre of supernatant. The second expression system utilised the high expression vector directly, Ig domains of the chosen immunoglobulin isotype were amplified from peripheral blood mononuclear cell (PBMC) RNA and ligated into the vector in frame with DNA encoding the antigen. We describe potential pitfalls that may be encountered while using Ig **fusion proteins** as immunogen and demonstrate ways in which to tailor their design for optimal mAb production.

L7 ANSWER 5 OF 5 MEDLINE on STN

2002410752. PubMed ID: 12165074. Coupling complement regulators to immunoglobulin domains generates effective anti-complement reagents with extended half-life in vivo. Harris C L; Williams A S; Linton S M; Morgan B P. (Department of Medical Biochemistry, University of Wales College of Medicine, Heath Park, Cardiff, UK.. HarrisCL@cardiff.ac.uk) . Clinical and experimental immunology, (2002 Aug) Vol. 129, No. 2, pp. 198-207. Journal code: 0057202. ISSN: 0009-9104. L-ISSN: 0009-9104.
Report No.: NLM-PMC1906445. Pub. country: England: United Kingdom.
Language: English.

AB Complement activation and subsequent generation of inflammatory molecules and membrane attack complex contributes to the pathology of a number of inflammatory and degenerative diseases, including arthritis, glomerulonephritis and demyelination. Agents that specifically inhibit complement activation might prove beneficial in the treatment of these diseases. Soluble recombinant forms of the naturally occurring membrane complement regulatory proteins (CRP) have been exploited for this purpose. We have undertaken to design better therapeutics based on CRP. Here we describe the generation of soluble, recombinant CRP comprising rat decay accelerating factor (**DAF**) or rat CD59 expressed as **Fc fusion proteins**, antibody-like molecules comprising two CRP moieties in place of the antibody Fab arms (CRP-Ig). Reagents bearing **DAF** on each arm (**DAF**-Ig), CD59 on each arm (CD59-Ig) and a hybrid reagent containing both **DAF** and CD59 were generated. All three reagents inhibited C activation in vitro. Compared with soluble CRP lacking **Fc** domains, activity was reduced, but was fully restored by enzymatic release of the regulator from the Ig moiety, implicating steric constraints in reducing functional activity. In vivo studies showed that **DAF**-Ig, when compared to soluble **DAF** , had a much extended half-life in the circulation in rats and concomitantly caused a sustained reduction in plasma complement activity. When given intra-articularly to rats in a model of arthritis, **DAF** -Ig significantly reduced severity of disease. The data demonstrate the potential of CRP-Ig as reagents for sustained therapy of inflammatory disorders, including arthritis, but emphasize the need for careful design of **fusion proteins** to retain function.

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L8 16 L2 AND CR1

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=> s l9 and pd<20040121
   1 FILES SEARCHED...
   4 FILES SEARCHED...
L10           6 L9 AND PD<20040121

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11           6 DUP REMOVE L10 (0 DUPLICATES REMOVED)

=> d l11 1-6 cbib abs

L11  ANSWER 1 OF 6  BIOSIS  COPYRIGHT (c) 2010 The Thomson Corporation  on STN
2004:150816  Document No.: PREV200400147153. ScFv-mediated targeting of
     complement regulatory proteins to the erythrocyte surface. Spitzer, Dirk
     [Reprint Author]; Krych-Goldberg, Malgorzata [Reprint Author]; Liszewski,
     Kathryn M. [Reprint Author]; Atkinson, John P. [Reprint Author]. Division
     of Rheumatology, Washington University School of Medicine, Saint Louis,
     MO, USA. Blood, (November 16 2003) Vol. 102, No. 11, pp. 503a.
     print.
     Meeting Info.: 45th Annual Meeting of the American Society of Hematology.
     San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
     CODEN: BLOOAW. ISSN: 0006-4971. Language: English.
AB   Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by red blood
     cell (RBC) lysis and hemoglobin accumulation in the urine.  Intravascular
     hemolysis occurs because of a deficit of two GPI-anchored complement
     regulatory proteins (CRPs) on these cells, CD59 and decay-accelerating
     factor (DAF, CD55).  As a means to restore a missing cell
     surface protein on a given cell or tissue, antibodies (Abs) or antibody
     fragments represent a powerful class of targeting moieties.  To attach a
     soluble CRP to the RBC membrane, we recently established a model system in
     which a single chain antibody fragment (scFv) specific for TER-119, an
     RBC-restricted surface antigen of the mouse was attached to the
     amino-terminus of secreted human DAF forms (Spitzer et al.,
     FASEB J. 17(7), Suppl., 2003).  In summary, RBCs from C57BL/6 mice loaded
     in vitro with this fusion proteins were significantly
     protected against lysis by human complement.  Following intravenous
     injection, these fusion proteins uniformly coated
     mouse RBCs, remained attached to the RBCs with a half-life similar to that
     of the target cell and reduced the sensitivity of these cells to lysis by
     human serum.  Thus, scFv-mediated targeting of proteins to a selected cell
     or tissue surface has promise as a means to supplement absent or defective
     plasma membrane constituents.  Based on these earlier findings, we report
     here the evaluation of three other human CRPs attached to the mouse RBC
     using the same scFv Ter-119 targeting approach: membrane cofactor protein
     (MCP; CD46), complement receptor 1 (CR1; CD35) and CD59.  While
     MCP and CR1 both act as cofactors for the factor I-mediated
     cleavage of an early step of the complement cascade (irreversible
     inactivation of C3b), CD59 inhibits formation of the membrane attack
     complex (MAC), the lytic final stage of this effector system.  A
     functional comparison of these four mouse RBC-targeted CRPs will be
     presented.  The results will be discussed with respect to finding the most
     promising candidate(s) suitable for a translation into an analogous system
     employing scFvs directed against human RBC-specific antigens as an
     additional option for the treatment of patients suffering from PNH.

L11  ANSWER 2 OF 6  HCAPLUS  COPYRIGHT 2010 ACS on STN
2002:51638   Document No. 136:101105  Membrane binding peptides of CD59 and
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DAF derivatives in targeting lipid rafts of cell membranes for treatment of inflammatory and immune disorders. Rowling, Pamela Jane Elizabeth; Smith, Geoffrey Paul; Ridley, Simon Hugh (Adprotech Limited, UK). PCT Int. Appl. WO 2002004638 A1 **20020117**, 51 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-GB3034 20010706. PRIORITY: GB 2000-16811 20000707.

AB The present invention provides membrane binding elements associated with a soluble derivative of complement regulatory polypeptides CD59 or **DAF** that bind lipid raft components for delivery of compds. to lipid rafts to modulate intracellular or extracellular activity. Hence, this invention can be used in the treatment of inflammatory and other immune disorders. A soluble derivative of CD59 or **DAF** is provided which is associated with two or more heterologous membrane binding peptides with low membrane affinity. These membrane binding elements are soluble in aqueous solution, and the elements are capable of interacting, independently and with thermodn. additivity with components of cellular or artificial membranes exposed to extracellular fluids. Specifically, the membrane binding elements target lipid raft components of the membrane and bind to the lipid rafts to localize the polypeptide at the lipid rafts. Thus, membrane binding elements mediate internalization of the proteins. Components of lipid rafts include one or more of phosphatidylserine, phosphatidyl glycerol, glycosphingolipids, cholesterol, GP1-anchored proteins associated with lipid rafts and other protein components of lipid rafts that may be found on the exo-plasmic cellular surface. Another embodiment of the invention provides soluble derivs. which include a derivatized antibody or antibody fragment which can provide a surrogate receptor localized at a lipid raft to divert a mediator interacting with a lipid raft receptor or which can neutralize a cofactor of the raft needed for signaling. Soluble derivs. also include chemical or biol. compds. that have fluorescent properties or compds. that can form chemical bonds with proteins, sugar groups or lipids with crosslinking groups, enzymes, enzyme substrates or inhibitors and are used to study patching behavior of membrane proteins and lipids in DIGs. Soluble proteins of the present invention can be linked to membrane binding elements by disulfide bonds. Soluble forms of proteins that are normally located in lipid rafts can be produced either by recombinant methods or isolated from human urine or plasma. These proteins can be treated with 2-iminothiolane and further reacted with a pyridylthio group linked to the membrane binding peptide. The membrane binding peptide may also be linked to the soluble protein by a C-terminal cysteine in the soluble protein.

L11 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2010 ACS on STN

1998:766227 Document No. 130:91287 Viral vectors encoding human complement inhibitors for use in gene therapy. Ito, Katsuhisa; Sakata, Tsuneaki; Hasegawa, Mamoru (Dinabeck Laboratory K. K., Japan). Jpn. Kokai Tokkyo Koho JP 10313865 A **19981202** Heisei, 15 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1997-125965 19970515.

AB Described are retrovirus-based vectors encoding membrane-binding type human complement inhibitors such as **DAF** (decay accelerating factor; CD55), MCP (CD46), **CR1** (CD35), or CD59; retrovirus-based vectors for catching the membrane-binding type complement inhibitors; and **fusion proteins** comprised of the extracellular domain of the inhibitors and the transmembrane domain (TM) of other membrane proteins;. Preparation of vector pCAGGS-**DAF**-TM expressing the **fusion protein** containing **DAF** and the TM of VSV-G

(vesicular stomatitis virus G-protein), transformation of human complements-sensitive mouse cell PA317/β-gal, and resistance to human complements of the transgenic mouse cells expressing **DAF**-TM were shown. The vectors are stable and thus are suitable for clin. use.

L11 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2010 ACS on STN
1995:538616 Document No. 122:263536 Original Reference No. 122:48125a,48128a Chimeric proteins which block complement activation. Ko, Jone Long; Higgins, Paul J.; Yeh, C. Grace (Cytomed, Inc., USA). PCT Int. Appl. WO 9508570 A1 **19950330**, 73 pp. DESIGNATED STATES: W: AU, CA, CN, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US10786 19940923. PRIORITY: US 1993-126596 19930924; US 1994-310416 19940922.

AB The present invention relates to novel chimeric proteins comprising a first and a second polypeptides which inhibit complement activation, linked to a second polypeptide which inhibits complement activation selecting from membrane cofactor protein (MCP), decay accelerating factor (**DAF**), complement receptor 1, factor H, C4b binding protein, or fragments. Nucleic acids encoding the novel chimeric proteins and methods for purifying the chimeric proteins and reducing inflammation with the administration of the chimeric proteins of the invention. In example, a recombinant gene encoding a complement receptor **fusion proteins**, e.g. MCP-MCP, MCP-**DAF** and **DAF**-MCP were mol. cloned and expressed, and a complement activation blocker, CAB-2, was purified and identified by ELISA. The protein cofactor and decay accelerating factor activities were confirmed and inhibition of complement-mediated lysis was tested.

L11 ANSWER 5 OF 6 MEDLINE on STN
1996025866. PubMed ID: 7594566. A novel bifunctional chimeric complement inhibitor that regulates C3 convertase and formation of the membrane attack complex. Fodor W L; Rollins S A; Guilmette E R; Setter E; Squinto S P. (Department of Molecular Development, Alexion Pharmaceuticals, Inc., New Haven, CT 06511, USA.) Journal of immunology (Baltimore, Md. : 1950), **(1995 Nov 1)** Vol. 155, No. 9, pp. 4135-8. Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Human cells express cell surface complement regulatory molecules that inhibit the activity of the C3/C5 convertases (**DAF**, MCP, **CR1**) or inhibit the membrane attack complex (CD59). A single molecule that inhibits both the convertase activity and formation of the membrane attack complex has never been characterized. To this end, we have developed two reciprocal chimeric complement inhibitors (CD, NH2-CD59-**DAF**-GPI; and DC, NH2-**DAF**-CD59-GPI) that contain the functional domains of decay accelerating factor (**DAF** ; CD55) and CD59. Cell surface expression of the CD and DC chimeric proteins was detected with **DAF**- and CD59-specific antisera. Cell surface C3d deposition was inhibited on cells expressing the chimeric molecules, thereby indicating that the **DAF** moiety was functional in both molecules. Conversely, Ab-blocking experiments demonstrated that only the DC molecule retained CD59 function. Therefore, the DC molecule represents a novel potent chimeric bifunctional complement inhibitor that retains the functional domains of two distinct complement regulatory molecules.

L11 ANSWER 6 OF 6 MEDLINE on STN
1996043299. PubMed ID: 7496432. [Expression and role of complement regulatory proteins on human gametes and pre-implantation embryos]. Expression et role des proteines regulatrices du complement a la surface des gametes et des embryons pre-implantatoires humains. Fenichel P; Cervoni F; Donzeau M; Hsi B L. (INSERM U 364, Faculte de medecine, Nice.) Contraception, fertilite, sexualite (1992), **(1995 Sep)** Vol. 23,

No. 9, pp. 576-80. Ref: 50. Journal code: 9314045. ISSN: 1165-1083. L-ISSN: 1165-1083. Pub. country: France. Language: French.

AB Human gametes and pre-implantation embryos express selectively several complement regulatory proteins. Membrane cofactor protein (MCP, CD46) and decay accelerating factor (**DAF**, CD55) are regulators for C3 convertases and protectin (CD59) is an inhibitor of the membrane attack complex. These three proteins were identified on human sperm and found to be functional. CD55 and CD59 were both expressed by the plasmic membrane of unfertilized oocytes and pre-implantation embryos. CD46 was not present on unfertilized oocytes but appeared at the 6/8 cell-stage embryo when human gene expression first occurs. Complement receptor 1 (**CR1**, CD35) and MHC class I antigens were not found on oocytes neither on embryos. Such a selective expression of complement regulatory proteins associated with the lack of MHC class I antigens may represent an immune protective mechanism by which human gametes and pre-implantation embryos escape from complement-mediated damage during their travel through the female genital tract. Indeed uterine, tubal and follicular fluids contain all the components of the complement cascade, including classical and alternative pathways. Nevertheless participation of CD46 and CD59 in cell to cell interaction during fertilization and/or implantation cannot be excluded. CD59 is an adhesive molecule involved in the rosette phenomena and CD46 has been described as the human receptor for measles virus, which binds through a **fusion protein**. Monoclonal antibodies raised against these two proteins (CD46 and CD59) are able to inhibit heterospecific fertilization between zona-free hamster oocytes and human spermatozoa suggesting the role of these proteins during fertilization.

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L12          9 L2 AND CD35

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PROCESSING COMPLETED FOR L12
L13          5 DUP REMOVE L12 (4 DUPLICATES REMOVED)

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L13 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2010 ACS on STN

2008:348068 Document No. 148:328850 Swine tissues expressing human complement regulatory factor **fusion proteins** with eliminated or reduced affinity to membrane fatty acid raft for transplantation. Miyagawa, Shuji (Osaka University, Japan). Jpn. Kokai Tokkyo Koho JP 2008061539 A 20080321, 14pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2006-240852 20060905.

AB Human complement regulatory factor **fusion proteins** with no or reduced affinity to membrane fatty acid raft are designed. The **fusion proteins** contain the transmembrane domain derived from hemagglutinin of human influenza virus (four specific peptides comprising 28 or 31 amino acids containing three serial alanine residues are claimed). The complement regulatory factor part in the **fusion proteins** is derived from **DAF** (CD55 antigen), MCP (CD46 antigen), CD59 antigen, CR1 (**CD35** antigen), factor H, factor I, C4bp, C1 inhibitor, Crry receptor, HSV-gCl (Herpes Simplex Virus type 1 glycoprotein gcl) or their fragment. When the **DAF** is used, its functional domains SCR2, SCR3 and SCR4 are included in the **fusion protein** constructs. The genes encoding the human complement regulatory factor **fusion proteins** are introduced into host swine cells (more specifically endothelium) for preparing transplant tissues. The transplant swine tissues expressing the complement regulatory factor **fusion proteins** show resistance to human serum to prevent rejection reaction. However, PERV (Porcine

Endogenous RetroVirus) that is potentially carried over from the original swine cells does not show resistance to human serum owing to the used transmembrane domain with no or reduced affinity to membrane fatty acid raft. The chance of PERV infection in host human is expected to be greatly reduced.

L13 ANSWER 2 OF 5 SCISEARCH COPYRIGHT (c) 2010 The Thomson Corporation on STN

2007:1121710 The Genuine Article (R) Number: 221AA. Transcriptional control of complement receptor gene expression.
Martin, Brian K. (Reprint). Univ Iowa, Grad Program Immunol, Dept Microbiol, 3-403 Bowen Sci Bldg, 51 Newton Rd, Iowa City, IA 52242 USA (Reprint). Martin, Brian K. (Reprint). Univ Iowa, Grad Program Immunol, Dept Microbiol, Iowa City, IA 52242 USA. E-mail: brian-martin@uiowa.edu.
IMMUNOLOGIC RESEARCH (2007) Vol. 39, No. 1-3, pp. 146-159. ISSN: 0257-277X. Publisher: HUMANA PRESS INC, 999 RIVERVIEW DRIVE SUITE 208, TOTOWA, NJ 07512 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Immune complement is a critical system in the immune response and protection of host cells from damage by complement is critical during inflammation. The expression of the receptors for the inflammatory anaphylatoxin molecules is also key in immunity. In order to fully appreciate the biology of complement, a basic understanding of the molecular regulation of complement receptor gene expression is critical, yet these kinds of studies are lacking for many genes. Importantly, recent genetic studies have demonstrated that promoter-enhancer polymorphisms can contribute to pathology in diseases such as atypical hemolytic uremic syndrome. This review will focus on what is currently known about the genetic regulation of key protective complement receptors genes including CR1 (**CD35**), CR2 (CD21), Crry, MCP (CD46), **DAF** (CD55), and CD59. In addition, the regulation of the anaphylatoxin receptors genes, C3aR and C5aR (CD88) will also be discussed. Since new research continuously uncovers novel functions for these proteins, a greater appreciation of the mechanisms involved in gene regulation will be critical for understanding the biology of these molecules.

L13 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN

2004:150816 Document No.: PREV200400147153. ScFv-mediated targeting of complement regulatory proteins to the erythrocyte surface. Spitzer, Dirk [Reprint Author]; Krych-Goldberg, Malgorzata [Reprint Author]; Liszewski, Kathryn M. [Reprint Author]; Atkinson, John P. [Reprint Author]. Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, USA. Blood, (November 16 2003) Vol. 102, No. 11, pp. 503a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by red blood cell (RBC) lysis and hemoglobin accumulation in the urine. Intravascular hemolysis occurs because of a deficit of two GPI-anchored complement regulatory proteins (CRPs) on these cells, CD59 and decay-accelerating factor (**DAF**, CD55). As a means to restore a missing cell surface protein on a given cell or tissue, antibodies (Abs) or antibody fragments represent a powerful class of targeting moieties. To attach a soluble CRP to the RBC membrane, we recently established a model system in which a single chain antibody fragment (scFv) specific for TER-119, an RBC-restricted surface antigen of the mouse was attached to the amino-terminus of secreted human **DAF** forms (Spitzer et al., FASEB J. 17(7), Suppl., 2003). In summary, RBCs from C57BL/6 mice loaded in vitro with this **fusion proteins** were significantly protected against lysis by human complement. Following intravenous injection, these **fusion proteins** uniformly coated

mouse RBCs, remained attached to the RBCs with a half-life similar to that of the target cell and reduced the sensitivity of these cells to lysis by human serum. Thus, scFv-mediated targeting of proteins to a selected cell or tissue surface has promise as a means to supplement absent or defective plasma membrane constituents. Based on these earlier findings, we report here the evaluation of three other human CRPs attached to the mouse RBC using the same scFv Ter-119 targeting approach: membrane cofactor protein (MCP; CD46), complement receptor 1 (CR1; **CD35**) and CD59. While MCP and CR1 both act as cofactors for the factor I-mediated cleavage of an early step of the complement cascade (irreversible inactivation of C3b), CD59 inhibits formation of the membrane attack complex (MAC), the lytic final stage of this effector system. A functional comparison of these four mouse RBC-targeted CRPs will be presented. The results will be discussed with respect to finding the most promising candidate(s) suitable for a translation into an analogous system employing scFvs directed against human RBC-specific antigens as an additional option for the treatment of patients suffering from PNH.

L13 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2010 ACS on STN
1998:766227 Document No. 130:91287 Viral vectors encoding human complement inhibitors for use in gene therapy. Ito, Katsuhisa; Sakata, Tsuneaki; Hasegawa, Mamoru (Dinabeck Laboratory K. K., Japan). Jpn. Kokai Tokkyo Koho JP 10313865 A 19981202 Heisei, 15 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1997-125965 19970515.

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L13 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 1
1996043299. PubMed ID: 7496432. [Expression and role of complement regulatory proteins on human gametes and pre-implantation embryos]. Expression et role des proteines regulatrices du complement a la surface des gametes et des embryons pre-implantatoires humains. Fenichel P; Cervoni F; Donzeau M; Hsi B L. (INSERM U 364, Faculte de medecine, Nice.) Contraception, fertilite, sexualite (1992), (1995 Sep) Vol. 23, No. 9, pp. 576-80. Ref: 50. Journal code: 9314045. ISSN: 1165-1083. L-ISSN: 1165-1083. Pub. country: France. Language: French.

AB Human gametes and pre-implantation embryos express selectively several complement regulatory proteins. Membrane cofactor protein (MCP, CD46) and decay accelerating factor (**DAF**, CD55) are regulators for C3 convertases and protectin (CD59) is an inhibitor of the membrane attack complex. These three proteins were identified on human sperm and found to be functional. CD55 and CD59 were both expressed by the plasmic membrane of unfertilized oocytes and pre-implantation embryos. CD46 was not present on unfertilized oocytes but appeared at the 6/8 cell-stage embryo when human gene expression first occurs. Complement receptor 1 (CR1, **CD35**) and MHC class I antigens were not found on oocytes neither on embryos. Such a selective expression of complement regulatory proteins associated with the lack of MHC class I antigens may represent an immune protective mechanism by which human gametes and pre-implantation embryos escape from complement-mediated damage during their travel through the female genital tract. Indeed uterine, tubal and follicular fluids contain all the components of the complement cascade, including classical and

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=> s l2 and membrane cofactor protein or CMP
L14 32010 L2 AND MEMBRANE COFACTOR PROTEIN OR CMP

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L15 8 L12 AND MEMBRANE COFACTOR PROTEIN

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PROCESSING COMPLETED FOR L15
L16 4 DUP REMOVE L15 (4 DUPLICATES REMOVED)

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L16 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2008:348068 Document No. 148:328850 Swine tissues expressing human complement regulatory factor **fusion proteins** with eliminated or reduced affinity to membrane fatty acid raft for transplantation. Miyagawa, Shuji (Osaka University, Japan). Jpn. Kokai Tokkyo Koho JP 2008061539 A 20080321, 14pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2006-240852 20060905.

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L16 ANSWER 2 OF 4 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2004:150816 Document No.: PREV200400147153. ScFv-mediated targeting of complement regulatory proteins to the erythrocyte surface. Spitzer, Dirk [Reprint Author]; Krych-Goldberg, Malgorzata [Reprint Author]; Liszewski, Kathryn M. [Reprint Author]; Atkinson, John P. [Reprint Author]. Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, USA. Blood, (November 16 2003) Vol. 102, No. 11, pp. 503a. print. Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

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L16 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 1
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L18         25 L17 AND PD<20040121

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L19 ANSWER 1 OF 16 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2004:150816 Document No.: PREV200400147153. ScFv-mediated targeting of complement regulatory proteins to the erythrocyte surface. Spitzer, Dirk [Reprint Author]; Krych-Goldberg, Malgorzata [Reprint Author]; Liszewski, Kathryn M. [Reprint Author]; Atkinson, John P. [Reprint Author]. Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, USA. Blood, (**November 16 2003**) Vol. 102, No. 11, pp. 503a. print.
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FASEB J. 17(7), Suppl., 2003). In summary, RBCs from C57BL/6 mice loaded in vitro with this **fusion proteins** were significantly protected against lysis by human complement. Following intravenous injection, these **fusion proteins** uniformly coated mouse RBCs, remained attached to the RBCs with a half-life similar to that of the target cell and reduced the sensitivity of these cells to lysis by human serum. Thus, scFv-mediated targeting of proteins to a selected cell or tissue surface has promise as a means to supplement absent or defective plasma membrane constituents. Based on these earlier findings, we report here the evaluation of three other human CRPs attached to the mouse RBC using the same scFv Ter-119 targeting approach: membrane cofactor protein (**MCP**; CD46), complement receptor 1 (CR1; CD35) and CD59. While **MCP** and CR1 both act as cofactors for the factor I-mediated cleavage of an early step of the complement cascade (irreversible inactivation of C3b), CD59 inhibits formation of the membrane attack complex (MAC), the lytic final stage of this effector system. A functional comparison of these four mouse RBC-targeted CRPs will be presented. The results will be discussed with respect to finding the most promising candidate(s) suitable for a translation into an analogous system employing scFvs directed against human RBC-specific antigens as an additional option for the treatment of patients suffering from PNH.

L19 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN

2001:338740 Document No. 134:348962 Transfection system and expression vectors used for recombinant production of heterologous proteins (such as CAB-2, CAB-4, uPAR, VEGF-D or viral glycoprotein) in mammalian and/or insect cells. Innis, Michael; Scott, Elizabeth (Chiron Corporation, USA). PCT Int. Appl. WO 2001032901 A1 **20010510**, 71 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31275 19991230. PRIORITY: US 1999-475460 19991230.

AB The invention provides a transfection system for recombinant production of heterologous proteins (such as CAB-2, CAB-4, uPAR, VEGF-D or a viral glycoprotein) in mammalian and/or insect cells. The invention relates that the transfection system comprises two DNA constructs (plasmids), which are used to transform said mammalian and/or insect cells. The first DNA construct (plasmid) contains a selectable marker, such as a functionally impaired neomycin phosphotransferase II gene (neo*), and a second marker, such as a dihydrofolate reductase gene (dhfr) which contains at least one disabling mutation in the 5' coding region. The second DNA construct (plasmid) contains the polynucleotide sequence encoding the heterologous protein, and a third selectable marker, such as a dhfr gene, which contains a mutation at the 3' coding region. The invention also relates that the DNA constructs (plasmids) contain Cytomegalovirus, Rous sarcoma virus and Simian virus 40 promoters, polyadenylation sites and origin of replications. The invention further relates that in cells transformed with said DNA constructs (plasmids) recombination occurs between the second and third selectable markers (the mutated dhfr genes), which results in cells being able to express the heterologous protein. The invention also provides the expression vectors used to transform said mammalian and/or insect cells. As way of illustration, the materials and methods claimed in this invention were used to recombinantly produce CAB2.1 and CAB4.2 in CHO cells.

L19 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN

2001:218835 Document No. 135:4306 Chimeric CD46/**DAF** molecules reveal a cryptic functional role for SCR1 of **DAF** in regulating

complement activation. Christiansen, D.; Loveland, B.; Kyriakou, P.; Lanteri, M.; Rubinstein, E.; Gerlier, D. (V.P.V., Immunite and Infections Virales, CNRS-UCBL UMR 5537, Faculte de Medecine Laennec, Lyon, 69372, Fr.). Molecular Immunology, Volume Date 2000, 37(12-13), 687-696 (English) **2001**. CODEN: MOIMD5. ISSN: 0161-5890. Publisher: Elsevier Science Ltd..

AB Chimeric proteins using membrane cofactor (CD46) and decay accelerating factor (**DAF** or CD55) were generated to further investigate the functional domains involved in the regulation of human serum complement. Following activation of the classical pathway, the isolated substitution of CD46 SCR III (+3DAF) exhibited a modest regulatory activity comparable to that of CD46. The isolated substitution of CD46 SCR IV (+4DAF), and the combined CD46 SCR III+IV substitutions (+3/4DAF) were essentially as efficient as **DAF**. No regulation of C3b deposition was observed with the combined CD46 SCR I+II substitutions (+1/2DAF). When tested after activation of the alternative pathway, both the +3DAF and +3/4DAF chimeras failed to regulate C3b deposition, while the +4DAF chimera still displayed some activity. In contrast to that observed following classical pathway activation, the +1/2DAF chimera exhibited a similar efficiency to wild type CD46 and **DAF** in controlling C3b deposition. Using SCR specific antibodies, the regulatory activity of the +1/2DAF chimera against the alternative pathway was mapped to the first three distal SCR (i.e. **DAF** 1, **DAF** 2 and CD46 III). These data demonstrate that several combinations of SCR domains from two related complement regulators can result in functional mols., and reveal a novel and cryptic functional role for **DAF** SCR1.

L19 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 1

2000324479. PubMed ID: 10868627. A recombinant soluble chimeric complement inhibitor composed of human CD46 and CD55 reduces acute cardiac tissue injury in models of pig-to-human heart transplantation. Kroshus T J; Salerno C T; Yeh C G; Higgins P J; Bolman R M 3rd; Dalmasso A P. (Department of Surgery and Laboratory Medicine and Pathology, University of Minnesota, Minneapolis 55455, USA.) Transplantation, **(2000 Jun 15)** Vol. 69, No. 11, pp. 2282-9. Journal code: 0132144. ISSN: 0041-1337. L-ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Inasmuch as complement plays a critical role in many pathological processes and in xenograft rejection, efficient complement inhibitors are of great interest. Because the membrane-associated complement inhibitors are very effective, recombinant soluble molecules have been generated. METHODS: We tested the efficacy of complement activation blocker-2 (CAB-2), a recombinant soluble chimeric protein derived from human decay accelerating factor (**DAF**, CD55) and membrane cofactor protein (**MCP**, CD46), in two models of pig-to-human xenotransplantation in which tissue injury is complement mediated. The in vitro model consisted of porcine aortic endothelial cells and human serum, and the ex vivo model consisted of a porcine heart perfused with human blood. RESULTS: In vitro, addition of CAB-2 to serum inhibited cytotoxicity and the deposition of C4b and iC3b on the endothelial cells. Ex vivo, addition of CAB-2 to human blood prolonged organ survival from 17.3 +/- 6.4 min in controls to 108 +/- 55.6 min with 910 nM (100 microg/ml) CAB-2 and 219.8 +/- 62.7 min with 1820 nM (200 microg/ml) CAB-2. CAB-2 also retarded the onset of increased coronary vascular resistance. The complement activity of the perfusate was reduced by CAB-2, as was the generation of C3a and SC5b-9. The myocardial tissues had similar deposition of IgG, IgM, and C1q; however, CAB-2 reduced the deposition of C3, C4, and C9. Hearts surviving >240 min demonstrated trace to no deposition of C9 and normal histologic architecture. CONCLUSION: These results indicate that CAB-2 can function as an inhibitor of complement activation and markedly reduce tissue injury in models of

pig-to-human xenotransplantation and thus may represent a useful therapeutic agent for xenotransplantation and other complement-mediated conditions.

L19 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1999:576798 Document No. 131:213109 Smallpox inhibitor of complement enzymes (SPICE) protein and methods of inhibiting complement activation. Rosengard, Ariella M.; Ahearn, Joseph M. (Johns Hopkins University, USA; The University of Pittsburgh of the Commonwealth of Pennsylvania). PCT Int. Appl. WO 9944625 A1 **19990910**, 88 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US4635 19990302. PRIORITY: US 1998-PV76821 19980303.
AB The invention provides a complement inhibitor derived from variola, called smallpox inhibitor of complement enzymes (SPICE) and SPICE-related proteins, such as **fusion proteins**. These proteins are useful in the treatment of complement-mediated conditions, such as hyperacute rejection of xenografts.

L19 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1999:359674 Document No. 131:14852 Recombinant murine retroviruses that are resistant to inactivation by the human complement system. Wirth, Dagmar; Spitzer, Dirk; Hauser, Hansjorg (Gesellschaft Fur Biotechnologische Forschung m.b.H/ (GBF), Germany). PCT Int. Appl. WO 9927121 A1 **19990603**, 27 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP7484 19981120. PRIORITY: EP 1997-120402 19971121.
AB Murine retroviruses are the most important transfer systems for human gene therapy, yet their application is currently limited. One of the major restrictions for an in vivo application resides in the problem that this virus type is sensitive to inactivation by human complement factors. The present invention overcomes this limitation by modifying murine retroviruses with a gene encoding a **fusion protein** between the receptor interacting domain of retroviral surface protein env and the catalytically active domains of human complement inactivation factors, which causes said retroviruses to be resistant to human complement inactivation. Specifically, genes/gene fragments encoding retroviral proteins SU, TM, amphotropic ENV 10 A 1, ENV 4070 A, ecotropic ENV, and GALV ENV were spliced with those encoding human complement inactivation factors CD55 (**DAF**), CD59, CD46 (**MCP**), and HRF. The chimeric env genes were expressed in complement-sensitive cells and specifically integrated into virus particles, thereby leading to the generation of cells and viruses that are fully resistant to complement attack. Thus, this strategy provides a tool for establishment of complement resistant cells and generation of viruses for in vivo gene therapy.

L19 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 2
1999374595. PubMed ID: 10446929. Complement-protected amphotropic retroviruses from murine packaging cells. Spitzer D; Hauser H; Wirth D. (Department of Gene Regulation and Differentiation, GBF-National Research Center for Biotechnology, Braunschweig, Germany.) Human gene therapy, **(1999 Jul 20)** Vol. 10, No. 11, pp. 1893-902. Journal code: 9008950. ISSN: 1043-0342. L-ISSN: 1043-0342. Pub. country: United States. Language: English.
AB The application of retroviruses generated from murine cells for in vivo gene therapy is restricted primarily because of the rapid inactivation of these viruses by the human complement system. To circumvent this disadvantageous property of murine retroviruses we have generated infectious amphotropic retroviruses that exhibit strong protection against human complement attack. The membrane of these viruses contains a

fusion protein, DAFF2A, that is composed of the catalytic domain of the human complement regulatory protein (CRP) decay-accelerating factor (**DAF**) and the envelope protein of the amphotropic murine leukemia virus (MuLV) 4070A (EnvA). The fusion of two other CRPs, **MCP** and CD59, to the same amphotropic Env moiety did not lead to equivalent results. The **fusion protein** DAFF2A was stably expressed in mouse NIH 3T3-based helper cells and independently identified with either alpha-**DAF** MAb or alpha-Env PAb on the cell membrane. Western blot analysis confirmed the expected molecular weight of the **fusion protein**. Viral titers obtained from NIH 3T3 helper cell pools were 5 x 10(5) CFU for wild-type amphotropic EnvA virus and 1 x 10(5) CFU for DAFF2A virus, respectively. By blocking the catalytic domain of **DAF** by pretreatment with alpha-**DAF** MAb DAFF2A, recombinant virions could be converted to wild-type with respect to sensitivity against human serum. Since the method for producing virions that are protected against human serum should be applicable to any cell type it offers a novel tool for human in vivo gene therapy.

L19 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1998:766227 Document No. 130:91287 Viral vectors encoding human complement inhibitors for use in gene therapy. Ito, Katsuhisa; Sakata, Tsuneaki; Hasegawa, Mamoru (Dinabeck Laboratory K. K., Japan). Jpn. Kokai Tokkyo Koho JP 10313865 A **19981202** Heisei, 15 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1997-125965 19970515.

AB Described are retrovirus-based vectors encoding membrane-binding type human complement inhibitors such as **DAF** (decay accelerating factor; CD55), **MCP** (CD46), CR1 (CD35), or CD59; retrovirus-based vectors for catching the membrane-binding type complement inhibitors; and **fusion proteins** comprised of the extracellular domain of the inhibitors and the transmembrane domain (TM) of other membrane proteins;. Preparation of vector pCAGGS-**DAF**-TM expressing the **fusion protein** containing **DAF** and the TM of VSV-G (vesicular stomatitis virus G-protein), transformation of human complements-sensitive mouse cell PA317/β-gal, and resistance to human complements of the transgenic mouse cells expressing **DAF**-TM were shown. The vectors are stable and thus are suitable for clin. use.

L19 ANSWER 9 OF 16 MEDLINE on STN
1998440612. PubMed ID: 9765493. Short consensus repeat domain 1 of decay-accelerating factor is required for enterovirus 70 binding. Karnauchow T M; Dawe S; Lublin D M; Dimock K. (Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5.) Journal of virology, **(1998 Nov)** Vol. 72, No. 11, pp. 9380-3. Journal code: 0113724. ISSN: 0022-538X. L-ISSN: 0022-538X. Report No.: NLM-PMC110365. Pub. country: United States. Language: English.

AB Enterovirus 70 (EV70), like several other human enteroviruses, can utilize decay-accelerating factor (**DAF** [CD55]) as an attachment protein. Using chimeric molecules composed of different combinations of the short consensus repeat domains (SCRs) of **DAF** and membrane cofactor protein (CD46), we show that sequences in SCR1 of **DAF** are essential for EV70 binding. Of the human enteroviruses that can bind to **DAF**, only EV70 and coxsackievirus A21 require sequences in SCR1 for this interaction.

L19 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1997:689510 Document No. 128:21875 Original Reference No. 128:4291a,4294a Chimeric proteins which block complement activation. Ko, Jone-long; Yeh, C. Grace (Cytomed, Inc., USA). U.S. US 5679546 A **19971021**, 31 pp., Cont.-in-part of U.S. Ser. No. 126,596,abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-310416 19940922. PRIORITY: US 1993-126596 19930924.

AB The present invention relates to novel chimeric proteins comprising a first polypeptide which inhibits complement activation, linked to a second polypeptide which inhibits complement activation, nucleic acids encoding novel chimeric proteins and methods of reducing inflammation with the administration of the chimeric proteins of the invention. The first and the second polypeptide are derived from membrane cofactor protein (**MCP**), decay accelerating factor (**DAF**), complement receptor 1, factor H, and C4b binding protein. Demonstrated were construction and expression of **MCP**-**DAF** pG3N plasmid, **MCP**-**MCP** pG3N plasmid, and **DAF**-**MCP** pII SK plasmid, and characterization of recombinant chimeric protein CAB-2.

L19 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1997:53764 Document No. 126:70155 Original Reference No. 126:13445a,13448a Complement-inhibiting fusion products of membrane cofactor protein and decay accelerating protein for treatment of complement-related disorders. Innis, Michael A.; Zaror, Isabel; Creasey, Abla A. (Chiron Corporation, USA). PCT Int. Appl. WO 9634965 A2 **19961107**, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US6301 19960503. PRIORITY: US 1995-435149 19950505.
AB **Fusion proteins** of membrane cofactor protein (**MCP**) and decay-accelerating factor (**DAF**) containing peptides capable of binding glycosaminoglycans and the chimeric genes encoding them are described for use in the treatment of complement-associated disorders. The glycosaminoglycan-binding peptides bind cell surface glycosaminoglycans such as heparin.

L19 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2010 ACS on STN
1995:538616 Document No. 122:263536 Original Reference No. 122:48125a,48128a Chimeric proteins which block complement activation. Ko, Jone Long; Higgins, Paul J.; Yeh, C. Grace (Cytomed, Inc., USA). PCT Int. Appl. WO 9508570 A1 **19950330**, 73 pp. DESIGNATED STATES: W: AU, CA, CN, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US10786 19940923. PRIORITY: US 1993-126596 19930924; US 1994-310416 19940922.
AB The present invention relates to novel chimeric proteins comprising a first and a second polypeptides which inhibit complement activation, linked to a second polypeptide which inhibits complement activation selecting from membrane cofactor protein (**MCP**), decay accelerating factor (**DAF**), complement receptor 1, factor H, C4b binding protein, or fragments. Nucleic acids encoding the novel chimeric proteins and methods for purifying the chimeric proteins and reducing inflammation with the administration of the chimeric proteins of the invention. In example, a recombinant gene encoding a complement receptor **fusion proteins**, e.g. **MCP**-**MCP**, **MCP**-**DAF** and **DAF**-**MCP** were mol. cloned and expressed, and a complement activation blocker, CAB-2, was purified and identified by ELISA. The protein cofactor and decay accelerating factor activities were confirmed and inhibition of complement-mediated lysis was tested.

L19 ANSWER 13 OF 16 MEDLINE on STN
1996025866. PubMed ID: 7594566. A novel bifunctional chimeric complement inhibitor that regulates C3 convertase and formation of the membrane attack complex. Fodor W L; Rollins S A; Guilmette E R; Setter E; Squinto S P. (Department of Molecular Development, Alexion Pharmaceuticals, Inc., New Haven, CT 06511, USA.) Journal of immunology (Baltimore, Md. : 1950),

(1995 Nov 1) Vol. 155, No. 9, pp. 4135-8. Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Human cells express cell surface complement regulatory molecules that inhibit the activity of the C3/C5 convertases (**DAF**, **MCP**, CR1) or inhibit the membrane attack complex (CD59). A single molecule that inhibits both the convertase activity and formation of the membrane attack complex has never been characterized. To this end, we have developed two reciprocal chimeric complement inhibitors (CD, NH2-CD59-**DAF**-GPI; and DC, NH2-**DAF**-CD59-GPI) that contain the functional domains of decay accelerating factor (**DAF**; CD55) and CD59. Cell surface expression of the CD and DC chimeric proteins was detected with **DAF**- and CD59-specific antisera. Cell surface C3d deposition was inhibited on cells expressing the chimeric molecules, thereby indicating that the **DAF** moiety was functional in both molecules. Conversely, Ab-blocking experiments demonstrated that only the DC molecule retained CD59 function. Therefore, the DC molecule represents a novel potent chimeric bifunctional complement inhibitor that retains the functional domains of two distinct complement regulatory molecules.

L19 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 3

1996043299. PubMed ID: 7496432. [Expression and role of complement regulatory proteins on human gametes and pre-implantation embryos]. Expression et role des proteines regulatrices du complement a la surface des gametes et des embryons pre-implantatoires humains. Fenichel P; Cervoni F; Donzeau M; Hsi B L. (INSERM U 364, Faculte de medecine, Nice.) Contraception, fertilite, sexualite (1992), **(1995 Sep)** Vol. 23, No. 9, pp. 576-80. Ref: 50. Journal code: 9314045. ISSN: 1165-1083. L-ISSN: 1165-1083. Pub. country: France. Language: French.

AB Human gametes and pre-implantation embryos express selectively several complement regulatory proteins. Membrane cofactor protein (**MCP**, CD46) and decay accelerating factor (**DAF**, CD55) are regulators for C3 convertases and protectin (CD59) is an inhibitor of the membrane attack complex. These three proteins were identified on human sperm and found to be functional. CD55 and CD59 were both expressed by the plasmic membrane of unfertilized oocytes and pre-implantation embryos. CD46 was not present on unfertilized oocytes but appeared at the 6/8 cell-stage embryo when human gene expression first occurs. Complement receptor 1 (CR1, CD35) and MHC class I antigens were not found on oocytes neither on embryos. Such a selective expression of complement regulatory proteins associated with the lack of MHC class I antigens may represent an immune protective mechanism by which human gametes and pre-implantation embryos escape from complement-mediated damage during their travel through the female genital tract. Indeed uterine, tubal and follicular fluids contain all the components of the complement cascade, including classical and alternative pathways. Nevertheless participation of CD46 and CD59 in cell to cell interaction during fertilization and/or implantation cannot be excluded. CD59 is an adhesive molecule involved in the rosette phenomena and CD46 has been described as the human receptor for measles virus, which binds through a **fusion protein**. Monoclonal antibodies raised against these two proteins (CD46 and CD59) are able to inhibit heterospecific fertilization between zona-free hamster oocytes and human spermatozoa suggesting the role of these proteins during fertilization.

L19 ANSWER 15 OF 16 MEDLINE on STN

1994194103. PubMed ID: 7511647. Expression of a hybrid complement regulatory protein, membrane cofactor protein decay accelerating factor on Chinese hamster ovary. Comparison of its regulatory effect with those of decay accelerating factor and membrane cofactor protein. Iwata K; Seya T; Ariga H; Nagasawa S. (Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.) Journal of immunology (Baltimore, Md. : 1950), **(1994 Apr 1)** Vol. 152, No. 7, pp. 3436-44. Journal code:

2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767. Pub. country: United States. Language: English.

AB C activation on the cell surface is supposedly regulated by membrane cofactor protein (**MCP**) and decay accelerating factor (**DAF**). These are complementary in function: **MCP** acts as a cofactor in factor I-mediated C3b and C4b inactivation, thus preventing the assembly of C3 convertases, whereas **DAF** accelerates spontaneous decay of the assembled C3 convertase. In this report, a hybrid **MCP-DAF** was expressed on Chinese hamster ovary cells by transfecting cDNA, and its regulatory activity was compared with those of **MCP** and **DAF** transfectants and with a transfectant expressing both **MCP** and **DAF** (**MCP** + **DAF**). The C3 deposition on sensitized CHO cells through activation of the classical pathway was blocked to a different degree with these transfectants, the order being **MCP** + **DAF** > **DAF** > hybrid **MCP-DAF** > **MCP**. Likewise, the C3 deposition via the alternative pathway was blocked efficiently in the order hybrid > **MCP** + **DAF** > **MCP**. The C-mediated cytolysis of CHO cells virtually reflected the degree of C3 fragment deposition. The **MCP-DAF** transfectant acquired additive protective activity against alternative pathway-mediated C3 deposition and cytolysis but was less potent in circumventing classical pathway attack than cells that expressed **DAF** alone or **DAF** + **MCP**. Hybrid **MCP-DAF** may be useful for alleviating C-mediated cell damage, especially via the alternative pathway.

L19 ANSWER 16 OF 16 MEDLINE on STN

1995027037. PubMed ID: 7524206. Effects of transfected complement regulatory proteins, **MCP**, **DAF**, and **MCP**/DAE hybrid, on complement-mediated swine endothelial cell lysis. Miyagawa S; Shirakura R; Iwata K; Nakata S; Matsumiya G; Izutani H; Matsuda H; Terado A; Matsumoto M; Nagasawa S; et al. (First Department of Surgery, Osaka University Medical School, Japan.) Transplantation, **(1994 Oct 15)** Vol. 58, No. 7, pp. 834-40. Journal code: 0132144. ISSN: 0041-1337. L-ISSN: 0041-1337. Pub. country: United States. Language: English.

AB We established several swine endothelial cell (SEC) lines, expressing human **MCP** (CD46), **DAF** (CD55), and **MCP**/**DAF** hybrid by transfection of cDNA, and assessed the function of these transfectant molecules on complement-mediated cell lysis as an in vitro hyperacute rejection model of swine to human discordant xenograft. Discordant organ xenografts are hyperacutely rejected by complement activation. Amelioration of complement-mediated lysis by these transfectant molecules was tested in each SEC line by lactate dehydrogenase assay. Naive swine endothelial cells were markedly damaged by human complement mainly via the classical pathway, activating only minimally the alternative pathway of human complement. Both **MCP** and **DAF** protected SEC from human complement attack in parallel with the expression density, with **DAF** being more effective than **MCP**. The **MCP**/**DAF** hybrid was more effective than **MCP** alone, and as effective as **DAF** in this system. The results suggest that the transfection of **DAF** or the **MCP**/**DAF** hybrid cDNA into organs to be transplanted could protect against hyperacute rejection.

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L21 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2007:350058 Document No. 146:378219 Transgenic ungulates, such as pigs, expressing CTLA4-Ig and uses thereof in xenotransplantation. Ayares, David Lee; Cooper, David K. C. (Revivicor, Inc., USA). PCT Int. Appl. WO 2007035213 A2 20070329, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US30842 20060809. PRIORITY: US 2005-706843P 20050809.
AB The present invention provides ungulates, including pigs, expressing CTLA4-Ig, as well as tissue, organs, cells and cell lines derived from such animals. Such animals, tissues, organs and cells can be used in research and medical therapy, including xenotransplantation. In addition, methods are provided to prepare organs, tissues and cells expressing the CTLA4-Ig for use in xenotransplantation, and nucleic acid constructs and vectors useful therein.

L21 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2006:100311 Document No. 144:184670 RAGE-Ig **fusion proteins** and therapeutic uses thereof. O'Keefe, Theresa; Luciano, Peter; Qin, Shixin (Critical Therapeutics, Inc., USA). PCT Int. Appl. WO 2006012415 A2 20060202, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US25877 20050720. PRIORITY: US 2004-589678P 20040720.
AB The present invention is drawn to **fusion proteins** comprising a Receptor for Advanced Glycation Endproducts (RAGE) and an Ig element. In some embodiments the **fusion protein** may also be bound to RAGE ligand or its RAGE-binding fragment, such as HMGB1 A box. The invention also encompasses methods of treating a condition characterized by activation of an inflammatory cytokine cascade comprising administering such **fusion proteins**. The invention is also drawn to nucleic acids encoding the **fusion proteins**, as well as vectors and cells comprising such nucleic acids. Provided are protein and cDNA sequences for RAGE-Ig **fusion proteins**.

L21 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:696571 Document No. 143:171338 Chimeric proteins comprising complement control protein repeats of **DAF**, CR1 and/or MCP, **IgG4** polypeptide and lipid tail for regulating complement activation. Medof, Edward; Kuttner-Kondo, Lisa (Case Western Reserve University, USA). PCT Int. Appl. WO 2005069726 A2 20050804, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,

VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB50257 20050121. PRIORITY: US 2004-537860P 20040121.

AB A hybrid complement-regulating protein comprises a first functional unit of a first complement regulatory protein having complement regulating properties, a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties and at least a second functional unit attached to the spacer sequence. The second functional unit may be a polypeptide providing a functional unit of a second complement regulatory protein, a polypeptide derived from an Ig, or a polypeptide that enhances binding of the protein to an animal cell. The hybrid protein may also contain a second spacer sequence and a third functional unit of a complement regulatory protein, a polypeptide derived from an Ig, and a polypeptide that enhances binding of the protein to an animal cell. The optional third functional unit may be the same or different from the first or second functional units. The functional units of complement regulatory protein are complement control protein repeats (CCPs) of decay-accelerating factor (**DAF**), complement receptor 1 (CR1) and membrane cofactor protein (MCP). The chimeric proteins are particularly useful for inhibiting excessive complement activation and for treating diseases such as reperfusion injury, stroke, septic shock, acute myocardial infarction, autoimmune disease, inflammatory bowel disease, etc.

=> s l2 and lipid tail
L22 1 L2 AND LIPID TAIL

=> d l22 cbib abs

L22 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2010 ACS on STN

2005:696571 Document No. 143:171338 Chimeric proteins comprising complement control protein repeats of **DAF**. CR1 and/or MCP, IgG4 polypeptide and **lipid tail** for regulating complement activation.

Medof, Edward; Kuttner-Kondo, Lisa (Case Western Reserve University, USA). PCT Int. Appl. WO 2005069726 A2 20050804, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB50257 20050121. PRIORITY: US 2004-537860P 20040121.

AB A hybrid complement-regulating protein comprises a first functional unit of a first complement regulatory protein having complement regulating properties, a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties and at least a second functional unit attached to the spacer sequence. The second functional unit may be a polypeptide providing a functional unit of a second complement regulatory protein, a polypeptide derived from an Ig, or a polypeptide that enhances binding of the protein to an animal cell. The hybrid protein may also contain a second spacer sequence and a third functional unit of a complement regulatory protein, a polypeptide derived from an Ig, and a polypeptide that enhances binding of the protein to an animal cell. The optional third functional unit may be the same or different from the first or second functional units. The functional units of complement regulatory protein are complement control protein repeats (CCPs) of decay-accelerating factor (**DAF**), complement receptor 1 (CR1) and membrane cofactor protein (MCP). The

chimeric proteins are particularly useful for inhibiting excessive complement activation and for treating diseases such as reperfusion injury, stroke, septic shock, acute myocardial infarction, autoimmune disease, inflammatory bowel disease, etc.

```
=> s "DAF-CR1B"
L23          0 "DAF-CR1B"

=> s "DAF-Ig4"
L24          0 "DAF-IG4"

=> s "DAF-MCP"
L25        156 "DAF-MCP"

=> s l25 and pd<20040121
   2 FILES SEARCHED...
L26        132 L25 AND PD<20040121

=> s l26 and "CCPs4-7"
L27          0 L26 AND "CCPS4-7"

=> dup remove l26
PROCESSING COMPLETED FOR L26
L28         44 DUP REMOVE L26 (88 DUPLICATES REMOVED)

=> s l28 and CCP
L29          0 L28 AND CCP

=> s l28 and short consensus repeat
L30          3 L28 AND SHORT CONSENSUS REPEAT

=> d l30 1-3 cbib abs

L30  ANSWER 1 OF 3     MEDLINE on STN
1999062246.    PubMed ID: 9844117.   Complement regulatory proteins in
     glomerular diseases. Nangaku M. (Division of Nephrology and Endocrinology,
     University of Tokyo School of Medicine, Tokyo, Japan..
     mnangaku-tky@umin.ac.jp) . Kidney international, (1998 Nov) Vol.
     54, No. 5, pp. 1419-28.  Ref: 112. Journal code: 0323470. ISSN: 0085-2538.
     L-ISSN: 0085-2538. Pub. country: United States. Language: English.
AB   Complement activation plays a critical role in the pathogenesis of many
     forms of glomerulonephritis.  Complement activation leads to tissue injury
     through various mechanisms including the generation of chemotactic factors
     and activation of the resident glomerular cells following C5b-9 insertion.
     Recent advances have disclosed the mechanisms of regulation of complement
     activation by discovery of a number of complement regulatory proteins.
     Decay accelerating factor (DAF), membrane cofactor protein (MCP), and
     complement receptor type 1 (CR1) act by inactivating C3/C5 convertase.
     They belong to the gene superfamily known as the regulators of complement
     activation (RCA), and share a common structural motif called a
     short consensus repeat (SCR).  In contrast,
     CD59 works by inhibiting formation of C5b-9.  The glomerulus is
     particularly well endowed with these membrane-bound complement regulatory
     proteins.  DAF, MCP, and CD59 are ubiquitously
     expressed by all three resident glomerular cells, while CR1 is localized
     exclusively in podocytes.  Expression of complement regulatory proteins
     can be changed by many factors including complement attack itself, and
     their expression levels are affected in various glomerular disorders.
     Studies utilizing cultured glomerular cells and animal models of
     glomerular diseases suggest important protective roles of complement
     regulatory proteins against immune-mediated renal injury.  Recent progress
```

in molecular biological techniques has made new therapeutic strategy feasible. Systemic administration of soluble recombinant complement regulatory proteins and local overexpression of complement regulatory proteins are promising therapeutic approaches.

L30 ANSWER 2 OF 3 MEDLINE on STN

1990009070. PubMed ID: 2978518. C3 receptors on macrophages. Law S K. (Department of Biochemistry, University of Oxford, UK.) Journal of cell science. Supplement, **(1988)** Vol. 9, pp. 67-97. Ref: 187. Journal code: 8502898. ISSN: 0269-3518. L-ISSN: 0269-3518. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The complement receptors on macrophage are responsible for their binding and ingestion of opsonized targets. The two established receptors are CR1, which recognizes C3b, and CR3, which recognizes iC3b, the natural product of C3b from cleavage by the complement control protein factor I and its cofactors. CR1 belongs to a group of proteins that contain a structural element characterized by its size of 60-65 amino acids, and four conservatively positioned cysteines, which engage in a self-contained 1-3, 2-4 disulphide arrangement. This structural unit is called SCR (**short consensus repeat**) and is found in the complement proteins C1r, C1s, C2, factor B, factor H, C4BP, **DAF**, **MCP** and CR2, each of which interacts with some cleavage products of C3 and/or C4. CR1 has 30 SCR units accounting for its entire extracellular structure. It has a transmembrane segment and a small cytoplasmic domain. CR3 is a heterodimer containing an alpha and beta subunit held together by non-covalent forces. The beta subunit is also found in the two leukocyte antigens, LFA-1 and p150,95, which have alpha subunits distinct from that of CR3. The beta subunit contains 56 cysteine residues, 42 of which lie in a span of 256 residues immediately adjacent to the transmembrane segment. It shares extensive sequence homology with subunits of membrane protein complexes that bind fibronectin and vitronectin, implicating that they all belong to an extended set of surface adhesion molecules not restricted to the immune system. p150,95 is also expressed on macrophages and it has iC3b binding activity. It also shares some functional properties with CR3 as an adhesion surface molecule.

L30 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN

1995:279792 Document No. 122:53630 Original Reference No. 122:10397a,10400a Mouse complement regulatory protein Crry/p65 uses the specific mechanisms of both human decay-accelerating factor and membrane cofactor protein. Kim, Youn-Uck; Kinoshita, Taroh; Molina, Hector; Hourcade, Dennis; Seya, Tsukasa; Wagner, Lynne M.; Holers, V. Michael (Dep. Immunoregulation., Res. Inst. Microbial Diseases, Osaka Univ., Osaka, 565, Japan). Journal of Experimental Medicine, 181(1), 151-9 (English) **1995**. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB Normal host cells are protected from the destructive action of complement by cell surface complement regulatory proteins. In humans, decay-accelerating factor (DAF) and membrane cofactor protein (MCP) play such a biol. role by inhibiting C3 and C5 convertases. DAF and MCP accomplish this task by specific mechanisms designated decay-accelerating activity and factor I cofactor activity, resp. In other species, including mice, structural and/or functional homologs of these proteins are not yet well characterized. Previous studies have shown that the mouse protein Crry/p65 has certain characteristics of self-protecting complement regulatory proteins. For example, Crry/p65 is expressed on a wide variety of murine cells, and when expressed on human K562 erythroleukemic cells, it prevents deposition of mouse C3 fragments on the cell surface during activation of either the classical or alternative complement pathway. The authors studied here factor I cofactor and decay-accelerating activities of Crry/p65. Recombinant Crry/p65 demonstrates cofactor activity for factor I-mediated cleavage of both

mouse C3b and C4b. Surprisingly, Crry/p65 also exhibits decay-accelerating activity for the classical pathway C3 convertase strongly and for the alternative pathway C3 convertase weakly. Therefore, mouse Crry/p65 uses the specific mechanisms of both human MCP and DAF. Although Crry/65, like MCP and DAF, contains tandem **short consensus repeats** (SCR) characteristic of C3/C4 binding proteins, Crry/p65 is not considered to be a genetic homolog of either MCP or DAF. Thus, Crry/p65 is an example of evolutionary conservation of two specific activities in a single unique protein in one species that are dispersed to individual proteins in another. The authors propose that the repeating SCR motif in this family has allowed this unusual process of evolution to occur, perhaps driven by the use of MCP and DAF as receptors by human pathogens such as the measles virus.

```
=> s CD55-Ig4
L31          0 CD55-IG4

=> s complement
L32     548347 COMPLEMENT

=> s l32 and regulatory protein
L33       7259 L32 AND REGULATORY PROTEIN

=> s l33 and "CCP"
L34         38 L33 AND "CCP"

=> s l34 and pd<20040121
   2 FILES SEARCHED...
L35         17 L34 AND PD<20040121

=> dup remove l35
PROCESSING COMPLETED FOR L35
L36          8 DUP REMOVE L35 (9 DUPLICATES REMOVED)

=> d l36 1-8 cbib abs

L36  ANSWER 1 OF 8  SCISEARCH  COPYRIGHT (c) 2010 The Thomson Corporation  on
     STN
2003:82389   The Genuine Article (R) Number: 634GG. CCP1-4 of the C4b-binding
     protein alpha-chain are required for factor I mediated cleavage of
     complement factor C3b.
     Blom A M (Reprint). Lund Univ, Wallenberg Lab, Dept Clin Chem, Malmo Univ
     Hosp, S-20502 Malmo, Sweden (Reprint). Kask L; Dahlback B.
     MOLECULAR IMMUNOLOGY (JAN 2003) Vol. 39, No. 10, pp. 547-556.
     ISSN: 0161-5890. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD,
     LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB        C4b-binding protein (C4BP) is a potent regulator of the
     complement system because it strongly inhibits the classical
     pathway of complement. Furthermore, C4BP serves as a cofactor
     to factor I (FI) in the cleavage of fluid phase C3b and can, therefore,
     influence the alternative pathway of complement. The major form
     of C4BP in plasma consists of seven identical alpha-chains and one
     beta-chain. Both types of subunits are composed of complement
     control protein (CCP) domains, eight such domains make up one
     alpha-chain. To elucidate the structural requirements for the interaction
     between Ob and the alpha-chain, nineteen recombinant C4BP variants were
     used: six truncated monomeric variants, nine polymeric variants in which
     individual CCPs were deleted, and finally four variants in which
     double alanine residues were introduced between CCPs. We found
     that C4BP requires all four N-terminal CCPs of the alpha-chain,
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with CCP2 and 3 being the most important, to act as a cofactor in the cleavage of C3b. Also, a cluster of positively charged amino acids on the interface between CCP1 and 2 is involved in the binding. Compared to the interaction with C4b, we conclude that binding of Ob to C4BP requires larger molecular surface on C4BP. We found that C4BP was able to act as cofactor in degradation of surface bound Ob and to accelerate decay of alternative C3-convertase. However, in both cases 1000-fold molar excess of C4BP over factor H (FH), well known inhibitor of the alternative pathway, was required to obtain the same effect.

L36 ANSWER 2 OF 8 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2002:609204 Document No.: PREV200200609204. Characterization of membrane cofactor protein (MCP, CD46) on spermatozoa: Role for a **complement regulatory protein** in fertilization. Riley, Rebecca C. [Reprint author]; Tannenbaum, Pamela; Abbott, Dave; Atkinson, John P. [Reprint author]. Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, USA. International Immunopharmacology, (**August, 2002**) Vol. 2, No. 9, pp. 1224. print.
Meeting Info.: XIX International Complement Workshop. Palermo, Italy. September 22-26, 2002.
ISSN: 1567-5769. Language: English.

L36 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2002:343997 Document No.: PREV200200343997. CCP1 of membrane cofactor protein (MCP, CD46) is retained in the testes of the common marmoset, a new world monkey: Role for a **complement regulatory protein** in fertilization. Riley, Rebecca C. [Reprint author]; Atkinson, John P. [Reprint author]. Division of Rheumatology, Washington University School of Medicine, 660 S. Euclid, Saint Louis, MO, 63110, USA. FASEB Journal, (**March 20, 2002**) Vol. 16, No. 4, pp. A683. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638. Language: English.
AB MCP, a widely expressed transmembrane protein, regulates the **complement** (C) cascade by inactivating the **complement** fragments C3b and C4b deposited on self-tissue. This activity resides in the N-terminal four **complement** control protein repeats (**CCPs**), with repeats 2-4 being required for C regulation. Antibodies to CCP1 of MCP, expressed on the inner acrosomal membrane of human sperm, inhibit binding of sperm to zona-free hamster eggs, indicating a role for MCP in fertilization. New world monkeys express an alternatively spliced form of MCP on most cells that lacks CCP1. This variant, while retaining C regulatory activity, may have an evolutionary advantage by rendering these monkeys non-susceptible to the measles virus, as the viral hemagglutinin requires CCP1 and CCP2 for attachment. We investigated the testes and sperm of the new world monkey Callithrix jacchus (the common marmoset) for the presence of CCP1. By PCR analysis CCP1 is present in testicular mRNA, and Western blots show CCP1 is included in MCP from the testes and sperm of the common marmoset. The tissue specific retention of CCP1 on sperm further suggests an evolutionarily conserved role for MCP in the fertilization process.

L36 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2001:265884 Document No.: PREV200100265884. **Complement regulatory protein** factor H in shark and carp. Moffat, B. E. [Reprint author]; Willis, A. C. [Reprint author]; Sim, R. B. [Reprint author]; Smith, S. L.. MRC Immunochemistry Unit, Oxford University, Oxford, OX4 3PQ, UK. FASEB Journal, (**March 7, 2001**) Vol. 15, No. 4, pp. A686. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA.

March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

AB Mammalian **complement** factor H is a 155kDa glycoprotein made up of 20 contiguous **CCP** domains, each about 60 amino acids long, containing 2 disulphide bridges. Factor H is a major regulator of turnover of the **complement** protein C3. Binding to anionic phospholipids is a general property of mammalian factor H. This binding activity was exploited to search for factor H-like proteins in non-mammalian vertebrates. The 45kDa plasma glycoprotein beta-2-glycoprotein 1 (APOH) is a homologue of FH. It consists of 5 **CCP** domains, and shares the phospholipid-binding properties of FH. Carp and shark sera were subjected to affinity chromatography on cardiolipin (CL) bound to porous glass beads. Mammalian FH, APOH and immunoglobulins typically bind to the immobilised CL, and are eluted in 1M NaCl. From carp serum, a protein of about 150kDa was eluted, and a 15-residue N-terminal sequence showed 7 identities to mammalian FH. No APOH-like protein was seen in carp. With shark serum, in addition to immunoglobulin, a major protein co-migrating on SDS-PAGE with human FH was eluted, but sequencing does not yet show conclusively that it is FH-like. A 42kDa shark protein was considered as a candidate for an APOH-like protein, but N-terminal sequencing showed a sequence motif PPP...EIV/L found in mammalian FH. In human serum, 2 proteins of 40-50kDa have been characterized;. FHL1 is an alternative splice product from the FH gene, while FHR is a product of a closely linked gene with high sequence identity to a region of FH. The 42kDa shark protein may, therefore, have a similar origin to the lower molecular weight human FHL or FHR proteins.

L36 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 1

2001227477. PubMed ID: 11243823. Solution structure and dynamics of the central **CCP** module pair of a poxvirus **complement** control protein. Henderson C E; Bromek K; Mullin N P; Smith B O; Uhrin D; Barlow P N. (The Edinburgh Centre for Protein Technology, the University of Edinburgh, the Joseph Black Chemistry Building, the King's Buildings, West Mains Road, Edinburgh EH9 3JJ, UK.) Journal of molecular biology, **(2001 Mar 16)** Vol. 307, No. 1, pp. 323-39. Journal code: 2985088R. ISSN: 0022-2836. L-ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB The **complement** control protein (**CCP**) module (also known as SCR, **CCP** or sushi domain) is prevalent amongst proteins that regulate **complement** activation. Functional and mutagenesis studies have shown that in most cases two or more neighbouring **CCP** modules form specific binding sites for other molecules. Hence the orientation in space of a **CCP** module with respect to its neighbours and the flexibility of the intermodular junction are likely to be critical for function. Vaccinia virus **complement** control protein (VCP) is a **complement regulatory protein** composed of four tandemly arranged **CCP** modules. The solution structure of the carboxy-terminal half of this protein (**CCP** modules 3 and 4) has been solved previously. The structure of the central portion (modules 2 and 3, VCP approximately 2,3) has now also been solved using NMR spectroscopy at 37 degrees C. In addition, the backbone dynamics of VCP approximately 2,3 have been characterised by analysis of its (15)N relaxation parameters. Module 2 has a typical **CCP** module structure while module 3 in the context of VCP approximately 2,3 has some modest but significant differences in structure and dynamics to module 3 within the 3,4 pair. Modules 2 and 3 do not share an extensive interface, unlike modules 3 and 4. Only two possible NOEs were identified between the bodies of the modules, but a total of 40 NOEs between the short intermodular linker of VCP approximately 2,3 and the bodies of the two modules determines a preferred, elongated, orientation of the two modules in the calculated structures. The anisotropy of rotational diffusion has been characterised from (15)N

relaxation data, and this indicates that the time-averaged structure is more compact than suggested by (1)H-(1)H NOEs. The data are consistent with the presence of many intermodular orientations, some of which are kinked, undergoing interconversion on a 10(-8)-10(-6) second time-scale. A reconstructed representation of modules 2-4 allows visualisation of the spatial arrangement of the 11 substitutions that occur in the more potent **complement** inhibitor from Variola (small pox) virus.

L36 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN DUPLICATE 2
2000:389100 Document No.: PREV200000389100. Conservation in decay accelerating factor (DAF) structure among primates. Kuttner-Kondo, Lisa; Subramanian, V. Bala; Atkinson, John P.; Yu, Jianliang; Medof, M. Edward [Reprint author]. Department of Pathology, School of Medicine, Case Western Reserve University, Institute of Pathology, 2085 Adelbert Road, Rm. 301, Cleveland, OH, 44106, USA. Developmental and Comparative Immunology, (**December, 2000**) Vol. 24, No. 8, pp. 815-827. print.
CODEN: DCIMDQ. ISSN: 0145-305X. Language: English.
AB The decay accelerating factor (DAF, CD55) protects self cells from activation of autologous **complement** on their surfaces. It functions to disable the C3 convertases, the central amplification enzymes of the cascade. Its active site(s) are contained within four apprx60 amino acid long units, termed **complement** control protein repeats (**CCPs**), which are suspended above the cell surface on a 68 amino acid long serine/threonine (S/T)-rich cushion that derives from three exons. We previously proposed a molecular model of human DAF's four **CCPs** in which certain amino acids were postulated to be recognition sites for the interaction between DAF and the C3 convertases. In the current study, we characterized DAF in five non-human primates: the great apes, gorilla and common chimpanzee, and the Old World monkeys: hamadryas baboon, Rhesus macaque, and patas monkey. Amino acid homology to human DAF was approximately 98% for the two great apes and 83% for the three Old World monkeys. The above cited putative ligand interactive residues were found to be fully conserved in all of the non-human primates, although there were amino acid changes outside of these areas. In the chimpanzee, alternative splicing of the S/T region was found potentially to be the source of multiple protein isoforms in erythrocytes, whereas in the patas monkey, similar alternative splicing was observed but only one protein band was seen. Interestingly, a Rhesus macaque was found to exhibit a phenomenon paralleling the human Cromer Dr(a-) blood group, in which a 44-base pair deletion in CCP3 leads to a frameshift and early STOP codon.

L36 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 3
1999334856. PubMed ID: 10408371. Viral **complement regulatory proteins**. Rosengard A M; Ahearn J M.
(Department of Pathology, University of Pennsylvania, USA.. aroseng@mail.med.upenn.edu) . Immunopharmacology, **(1999 May)** Vol. 42, No. 1-3, pp. 99-106. Ref: 61. Journal code: 7902474. ISSN: 0162-3109. L-ISSN: 0162-3109. Pub. country: Netherlands. Language: English.
AB The inactivation of **complement** provides cells and tissues critical protection from **complement**-mediated attack and decreases the associated recruitment of other inflammatory mediators. In an attempt to evade the host immune response, viruses have evolved two mechanisms to acquire **complement regulatory proteins**. They can directly seize the host cell **complement** regulators onto their outer envelope and/or they can produce their own proteins which are either secreted into the neighboring intercellular space or expressed as membrane-bound proteins on the infected host cell. The following review will concentrate on the viral

homologues of the mammalian **complement regulatory proteins**, specifically those containing **complement** control protein (**CCP**) repeats.

L36 ANSWER 8 OF 8 SCISEARCH COPYRIGHT (c) 2010 The Thomson Corporation on STN
1991:59929 The Genuine Article (R) Number: EV178. SECONDARY STRUCTURE OF A **COMPLEMENT** CONTROL PROTEIN MODULE BY 2-DIMENSIONAL H-1-NMR.
BARLOW P N (Reprint); BARON M; NORMAN D G; DAY A J; WILLIS A C; SIM R B; CAMPBELL I D. UNIV OXFORD, DEPT BIOCHEM, MRC, IMMUNOCHEM UNIT, S PARKS RD, OXFORD OX1 3QU, ENGLAND.
BIOCHEMISTRY (**29 JAN 1991**) Vol. 30, No. 4, pp. 997-1004. ISSN: 0006-2960. Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The **complement** control protein (**CCP**) module (also known as the short consensus repeat) is a consensus sequence of about 60 amino acid residues which is thought to fold independently. It occurs over 140 times in more than 20 extracellular mosaic proteins including 12 proteins of the **complement** cascade. An isolated **CCP** module, the 16th repeat from human **complement** factor H, has been expressed in a yeast vector and shown to fold with the same pattern of disulfide bond formation as is seen in the native protein. Two-dimensional 600-MHz H-1 NMR spectra of this module have been recorded at pH 3.3 and 6.0 and analyzed to permit determination of secondary structure in solution. The **CCP** module comprises two predominantly extended segments (Glu 1-His 13 and Ala 17-Glu27), two segments of double-stranded antiparallel beta-sheet (Gly 14-Val16 paired with Tyr31-Cys33 and Gly38-Asp40 paired with Ser57-Ile59), and a short piece of triple-stranded beta-sheet (Glu27-Thr30, Ile44-Leu48, and Lys51-Ser53). Turns occur at Asp22, Gly36, and Glu50, while Gly41-Ala43 appear to form a looped-out segment or bulge. This structure is compared with a secondary structure prediction made on the basis of an alignment scheme of 101 sequences for **CCP** modules [Perkins, S. J., Haris, P. I., Sim, R. B., & Chapman, D. (1988) Biochemistry 27, 4004-4012]-the experimentally determined secondary structure bears an overall resemblance to the predicted one but differs in the number and position of turns. Some of those amino acid residues which are highly conserved throughout the range of **CCP** modules appear to play a role in stabilizing the global fold.

```
=> s (medof e?/au or kuttner-kondo l?/au)
L37        100 (MEDOF E?/AU OR KUTTNER-KONDO L?/AU)

=> s l37 and complememt
L38          0 L37 AND COMPLEMEMT

=> s l37 and DAF
L39         67 L37 AND DAF

=> s l39 and chimera
L40          0 L39 AND CHIMERA

=> s l39 and chimeric
L41          1 L39 AND CHIMERIC

=> d l41 cbib abs

L41  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2010 ACS on STN
2005:696571   Document No. 143:171338  Chimeric proteins comprising
     complement control protein repeats of DAF. CR1 and/or MCP, IgG4
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polypeptide and lipid tail for regulating complement activation. **Medof, Edward; Kuttner-Kondo, Lisa** (Case Western Reserve University, USA). PCT Int. Appl. WO 2005069726 A2 20050804, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB50257 20050121. PRIORITY: US 2004-537860P 20040121.

AB A hybrid complement-regulating protein comprises a first functional unit of a first complement regulatory protein having complement regulating properties, a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties and at least a second functional unit attached to the spacer sequence. The second functional unit may be a polypeptide providing a functional unit of a second complement regulatory protein, a polypeptide derived from an Ig, or a polypeptide that enhances binding of the protein to an animal cell. The hybrid protein may also contain a second spacer sequence and a third functional unit of a complement regulatory protein, a polypeptide derived from an Ig, and a polypeptide that enhances binding of the protein to an animal cell. The optional third functional unit may be the same or different from the first or second functional units. The functional units of complement regulatory protein are complement control protein repeats (CCPs) of decay-accelerating factor (**DAF**), complement receptor 1 (CR1) and membrane cofactor protein (MCP). The **chimeric** proteins are particularly useful for inhibiting excessive complement activation and for treating diseases such as reperfusion injury, stroke, septic shock, acute myocardial infarction, autoimmune disease, inflammatory bowel disease, etc.

=> s l39 and fusion
L42 1 L39 AND FUSION

=> d l42 cbib abs

L42 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:696571 Document No. 143:171338 Chimeric proteins comprising complement control protein repeats of **DAF**. CR1 and/or MCP, IgG4 polypeptide and lipid tail for regulating complement activation. **Medof, Edward; Kuttner-Kondo, Lisa** (Case Western Reserve University, USA). PCT Int. Appl. WO 2005069726 A2 20050804, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB50257 20050121. PRIORITY: US 2004-537860P 20040121.

AB A hybrid complement-regulating protein comprises a first functional unit of a first complement regulatory protein having complement regulating properties, a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties and at least a second functional unit attached to the spacer sequence. The second functional unit may be a polypeptide providing a

functional unit of a second complement regulatory protein, a polypeptide derived from an Ig, or a polypeptide that enhances binding of the protein to an animal cell. The hybrid protein may also contain a second spacer sequence and a third functional unit of a complement regulatory protein, a polypeptide derived from an Ig, and a polypeptide that enhances binding of the protein to an animal cell. The optional third functional unit may be the same or different from the first or second functional units. The functional units of complement regulatory protein are complement control protein repeats (CCPs) of decay-accelerating factor (**DAF**), complement receptor 1 (CR1) and membrane cofactor protein (MCP). The chimeric proteins are particularly useful for inhibiting excessive complement activation and for treating diseases such as reperfusion injury, stroke, septic shock, acute myocardial infarction, autoimmune disease, inflammatory bowel disease, etc.

=> s l39 and CD55
L43 18 L39 AND CD55

=> s l43 and complement receptor 1
L44 1 L43 AND COMPLEMENT RECEPTOR 1

=> d l44 cbib abs

L44 ANSWER 1 OF 1 MEDLINE on STN
2002054064. PubMed ID: 11694537. Decay-accelerating factor (**DAF**), **complement receptor 1** (CR1), and factor H dissociate the complement AP C3 convertase (C3bBb) via sites on the type A domain of Bb. Hourcade Dennis E; Mitchell Lynne; **Kuttner-Kondo Lisa A**; Atkinson John P; Medof M Edward. (Washington University School of Medicine, Department of Medicine, Division of Rheumatology, St. Louis, Missouri 63110, USA.. dhourcad@im.wustl.edu) . The Journal of biological chemistry, (2002 Jan 11) Vol. 277, No. 2, pp. 1107-12. Electronic Publication: 2001-11-02. Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258. Pub. country: United States. Language: English.
AB The AP C3 convertase, C3bBb(Mg(2+)), is subject to irreversible dissociation (decay acceleration) by three proteins: **DAF**, CR1, and factor H. We have begun to map the factor B (fB) sites critical to these interactions. We generated a panel of fB mutations, focusing on the type A domain because it carries divalent cation and C3b-binding elements. C3bBb complexes were assembled with the mutants and subjected to decay acceleration. Two critical fB sites were identified with a structural model. 1) Several mutations centered at adjacent alpha helices 4 and 5 (Gln-335, Tyr-338, Ser-339, Asp-382) caused substantial resistance to **DAF** and CR1-mediated decay acceleration but not factor H. 2) Several mutations centered at the alpha 1 helix and adjoining loops (especially D254G) caused resistance to decay acceleration mediated by all three regulators and also increased C3b-binding affinity and C3bBb stability. In the simplest interpretation of these results, **DAF** and CR1 directly interact with C3bBb at alpha 4/5; factor H likely interacts at some other location, possibly on the C3b subunit. Mutations at the C3b.Bb interface interfere with the normal dissociation of C3b from Bb, whether it is spontaneous or promoted by **DAF**, CR1, or factor H.

=> s l43 and MCP
L45 0 L43 AND MCP

=> s l43 and CR1
L46 1 L43 AND CR1

=> d l46 cbib abs

L46 ANSWER 1 OF 1 MEDLINE on STN
2002054064. PubMed ID: 11694537. Decay-accelerating factor (**DAF**), complement receptor 1 (**CR1**), and factor H dissociate the complement AP C3 convertase (C3bBb) via sites on the type A domain of Bb. Hourcade Dennis E; Mitchell Lynne; **Kuttner-Kondo Lisa A**; Atkinson John P; Medof M Edward. (Washington University School of Medicine, Department of Medicine, Division of Rheumatology, St. Louis, Missouri 63110, USA.. dhourcad@im.wustl.edu) . The Journal of biological chemistry, (2002 Jan 11) Vol. 277, No. 2, pp. 1107-12. Electronic Publication: 2001-11-02. Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The AP C3 convertase, C3bBb(Mg(2+)), is subject to irreversible dissociation (decay acceleration) by three proteins: **DAF**, **CR1**, and factor H. We have begun to map the factor B (fB) sites critical to these interactions. We generated a panel of fB mutations, focusing on the type A domain because it carries divalent cation and C3b-binding elements. C3bBb complexes were assembled with the mutants and subjected to decay acceleration. Two critical fB sites were identified with a structural model. 1) Several mutations centered at adjacent alpha helices 4 and 5 (Gln-335, Tyr-338, Ser-339, Asp-382) caused substantial resistance to **DAF** and **CR1**-mediated decay acceleration but not factor H. 2) Several mutations centered at the alpha 1 helix and adjoining loops (especially D254G) caused resistance to decay acceleration mediated by all three regulators and also increased C3b-binding affinity and C3bBb stability. In the simplest interpretation of these results, **DAF** and **CR1** directly interact with C3bBb at alpha 4/5; factor H likely interacts at some other location, possibly on the C3b subunit. Mutations at the C3b.Bb interface interfere with the normal dissociation of C3b from Bb, whether it is spontaneous or promoted by **DAF**, **CR1**, or factor H.

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PROCESSING COMPLETED FOR L43
L47 10 DUP REMOVE L43 (8 DUPLICATES REMOVED)

=> d l47 1-10 cbib abs

L47 ANSWER 1 OF 10 MEDLINE on STN DUPLICATE 1
2007355477. PubMed ID: 17395591. Structure-based mapping of **DAF** active site residues that accelerate the decay of C3 convertases. **Kuttner-Kondo Lisa**; Hourcade Dennis E; Anderson Vernon E; Muqim Nasima; Mitchell Lynne; Soares Dinesh C; Barlow Paul N; Medof M Edward. (Institute of Pathology and Department of Biochemistry, Case Western Reserve University, Cleveland, Ohio 44106, USA.) The Journal of biological chemistry, (2007 Jun 22) Vol. 282, No. 25, pp. 18552-62. Electronic Publication: 2007-03-29. Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Focused complement activation on foreign targets depends on regulatory proteins that decay the bimolecular C3 convertases. Although this process is central to complement control, how the convertases engage and disassemble is not established. The second and third complement control protein (CCP) modules of the cell surface regulator, decay-accelerating factor (**DAF**, **CD55**), comprise the simplest structure mediating this activity. Positioning the functional effects of 31 substitution mutants of **DAF** CCP2 to -4 on partial structures was previously reported. In light of the high resolution crystal structure of the **DAF** four-CCP functional region, we now reexamine the effects of these and 40 additional mutations. Moreover, we map six monoclonal

antibody epitopes and overlap their effects with those of the amino acid substitutions. The data indicate that the interaction of **DAF** with the convertases is mediated predominantly by two patches approximately 13 A apart, one centered around Arg69 and Arg96 on CCP2 and the other around Phe148 and Leu171 on CCP3. These patches on the same face of the adjacent modules bracket an intermodular linker of critical length (16 A.) Although the key **DAF** residues in these patches are present or there are conservative substitutions in all other C3 convertase regulators that mediate decay acceleration and/or provide factor I-cofactor activity, the linker region is highly conserved only in the former. Intra-CCP regions also differ. Linker region comparisons suggest that the active CCPs of the decay accelerators are extended, whereas those of the cofactors are tilted. Intra-CCP comparisons suggest that the two classes of regulators bind different regions on their respective ligands.

L47 ANSWER 2 OF 10 MEDLINE on STN
2006056200. PubMed ID: 16421483. Decay-accelerating factor prevents acute humoral rejection induced by low levels of anti-alphaGal natural antibodies. Shimizu Ichiro; Smith Neal R; Zhao Guiling; **Medof Edward**; Sykes Megan. (Transplantation Biology Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02129, USA.) Transplantation, (2006 Jan 15) Vol. 81, No. 1, pp. 95-100. Journal code: 0132144. ISSN: 0041-1337. L-ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Hyperacute and delayed vascular rejection due to natural antibodies (NAb) present major obstacles in pig-to-primate xenotransplantation. Although "supraphysiologic" expression of human complement regulatory proteins (CRPs) can prevent hyperacute rejection in discordant xenogenic recipients, their physiologic role in the homologous setting is undefined. We have evaluated the effect of the absence of decay-accelerating factor (**DAF**) on cardiac allograft rejection in the presence of different levels of antidonor antibodies (Ab). METHODS: DAF1-deficient (**DAF** KO; B6129F2 H-2) mice were used as heart graft donors to alpha1,3-galactosyltransferase deficient (GalT KO; B6, H-2) recipients. Heterotopic heart grafting was performed with or without presensitization. Graft survival, histology, and anti-alphaGal Ab levels were monitored. RESULTS: **DAF** knockout (KO) but not wild-type (WT) grafts showed hyperacute or acute humoral rejection in nonsensitized GalT KO mice with low levels of anti-alphaGal IgM NAb. However, humoral rejection of both **DAF** KO and **DAF** WT donor grafts occurred in presensitized GalT KO recipients. CONCLUSIONS: The expression of **DAF** prevents hyperacute rejection in mice with low titers of anti-alphaGal antibody. These studies demonstrate the physiologic role of **DAF** in preventing humoral rejection in the presence of low levels of NAb and have implications for transplantation of discordant vascularized xenografts.

L47 ANSWER 3 OF 10 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2006:222835 Document No.: PREV200600221822. Complement contributes to increased hepatic ICAM-1 expression during chronic ethanol-induced early liver injury in mice. Pritchard, Michele T. [Reprint Author]; McMullen, Megan R.; Wang, QiFang; Cohen, Jessica I.; Stavitsky, Abram B.; Lin, Feng; **Medof, Edward**; Nagy, Laura E.. Case Western Reserve Univ, Cleveland, OH 44106 USA. Journal of Leukocyte Biology, (2005) No. Suppl. S, pp. 65.
Meeting Info.: 38th Annual Meeting of the Society-for-Leukocyte-Biology. Oxford, ENGLAND. September 21 -24, 2005. Soc Leukocyte Biol.
CODEN: JLBIE7. ISSN: 0741-5400. Language: English.

L47 ANSWER 4 OF 10 MEDLINE on STN
2002054064. PubMed ID: 11694537. Decay-accelerating factor (**DAF**

), complement receptor 1 (CR1), and factor H dissociate the complement AP C3 convertase (C3bBb) via sites on the type A domain of Bb. Hourcade Dennis E; Mitchell Lynne; **Kuttner-Kondo Lisa A**; Atkinson John P; Medof M Edward. (Washington University School of Medicine, Department of Medicine, Division of Rheumatology, St. Louis, Missouri 63110, USA.. dhourcad@im.wustl.edu) . The Journal of biological chemistry, (2002 Jan 11) Vol. 277, No. 2, pp. 1107-12. Electronic Publication: 2001-11-02. Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The AP C3 convertase, C3bBb(Mg(2+)), is subject to irreversible dissociation (decay acceleration) by three proteins: **DAF**, CR1, and factor H. We have begun to map the factor B (fB) sites critical to these interactions. We generated a panel of fB mutations, focusing on the type A domain because it carries divalent cation and C3b-binding elements. C3bBb complexes were assembled with the mutants and subjected to decay acceleration. Two critical fB sites were identified with a structural model. 1) Several mutations centered at adjacent alpha helices 4 and 5 (Gln-335, Tyr-338, Ser-339, Asp-382) caused substantial resistance to **DAF** and CR1-mediated decay acceleration but not factor H. 2) Several mutations centered at the alpha 1 helix and adjoining loops (especially D254G) caused resistance to decay acceleration mediated by all three regulators and also increased C3b-binding affinity and C3bBb stability. In the simplest interpretation of these results, **DAF** and CR1 directly interact with C3bBb at alpha 4/5; factor H likely interacts at some other location, possibly on the C3b subunit. Mutations at the C3b.Bb interface interfere with the normal dissociation of C3b from Bb, whether it is spontaneous or promoted by **DAF**, CR1, or factor H.

L47 ANSWER 5 OF 10 MEDLINE on STN

2001443858. PubMed ID: 11490001. Characterization of the active sites in decay-accelerating factor. **Kuttner-Kondo L A**; Mitchell L; Hourcade D E; Medof M E. (Department of Pathology, Case Western Reserve University, Cleveland, OH 44106, USA.) Journal of immunology (Baltimore, Md. : 1950), (2001 Aug 15) Vol. 167, No. 4, pp. 2164-71. Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Decay-accelerating factor (**DAF**) is a complement regulator that dissociates autologous C3 convertases, which assemble on self cell surfaces. Its activity resides in the last three of its four complement control protein repeats (CCP2-4). Previous modeling on the nuclear magnetic resonance structure of CCP15-16 in the serum C3 convertase regulator factor H proposed a positively charged surface area on CCP2 extending into CCP3, and hydrophobic moieties between CCPs 2 and 3 as being primary convertase-interactive sites. To map the residues providing for the activity of **DAF**, we analyzed the functions of 31 primarily alanine substitution mutants based in part on this model. Replacing R69, R96, R100, and K127 in the positively charged CCP2-3 groove or hydrophobic F148 and L171 in CCP3 markedly impaired the function of **DAF** in both activation pathways. Significantly, mutations of K126 and F169 and of R206 and R212 in downstream CCP4 selectively reduced alternative pathway activity without affecting classical pathway activity. Rhesus macaque **DAF** has all the above human critical residues except for F169, which is an L, and its CCPs exhibited full activity against the human classical pathway C3 convertase. The recombinants whose function was preferentially impaired against the alternative pathway C3bBb compared with the classical pathway C4b2a were tested in classical pathway C5 convertase (C4b2a3b) assays. The effects on C4b2a and C4b2a3b were comparable, indicating that **DAF** functions similarly on the two enzymes. When CCP2-3 of **DAF** were oriented according to the crystal structure of CCP1-2 of membrane cofactor protein, the essential residues formed a contiguous region, suggesting a similar spatial

relationship.

L47 ANSWER 6 OF 10 MEDLINE on STN
2001162614. PubMed ID: 11262607. Release of complement regulatory proteins from ocular surface cells in infections. Cocuzzi E; Guidubaldi J; Bardenstein D S; Chen R; Jacobs M R; **Medof E M.** (Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA.) Current eye research, (2000 Nov) Vol. 21, No. 5, pp. 856-66. Journal code: 8104312. ISSN: 0271-3683. L-ISSN: 0271-3683. Pub. country: England: United Kingdom. Language: English.
AB PURPOSE: The decay accelerating factor (**DAF** or **CD55**) and the membrane inhibitor of reactive lysis (MIRL or CD59), two complement regulatory proteins that protect self cells from autologous complement-mediated injury, are attached to corneal and cqonjunctival epithelial cells by glycosylphos-phatidylinositol (GPI) anchors. We sought to 1) determine the frequency with which bacteria recovered from patients with infections of the eye elaborate factors that can remove these surface proteins from ocular cells, 2) determine the spectrum of bacteria from other sites that have similar effects, and 3) establish the time interval required for reconstitution of the two regulators. METHODS: Culture supernatants of 18 ocular isolates [P. aeruginosa (n = 3), S. marcescens (n = 1), S. epidermidis (n = 9), and S. aureus (n = 5)], and > 100 other clinical specimens isolated in the hospital's microbiology laboratory [P. mirabilis (n = 1), S. aureus (n = 65), S. epidermidis (n = 24), B. cereus (n = 12), H. influenzae (n = 15), and Enterobacter sp. (n = 21)] were incubated at 37 degrees C for various times with conjunctival epithelial cells, conjunctival fibroblasts or HeLa cells and the release of **DAF** and CD59 proteins from the surfaces of the cells analyzed by 2-site immunoradiometric assays and by Western blotting. The kinetics of recovery of **DAF** and CD59 expression on the cells was measured by flow cytometry. RESULTS: **DAF** and/or CD59 release from the cell monolayers varied from < 5% to > 99% at as much as a 1:81 dilution of the supernatant from some bacteria. On conjunctival epithelial cells, more than 8 hr was required for 44% recovery of **DAF** expression and for 50% recovery of CD59 expression. CONCLUSIONS: Bacteria produce phospholipases and/or other enzymes which can efficiently remove **DAF** and CD59 from ocular cell surfaces. This phenomenon may correlate with their in vivo pathogenicity.

L47 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 2
2000412170. PubMed ID: 10906393. Conservation in decay accelerating factor (**DAF**) structure among primates. **Kuttner-Kondo L;** Subramanian V B; Atkinson J P; Yu J; Medof M E. (Department of Pathology, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106, USA.) Developmental and comparative immunology, (2000 Dec) Vol. 24, No. 8, pp. 815-27. Journal code: 7708205. ISSN: 0145-305X. L-ISSN: 0145-305X. Pub. country: United States. Language: English.
AB The decay accelerating factor (**DAF**, **CD55**) protects self cells from activation of autologous complement on their surfaces. It functions to disable the C3 convertases, the central amplification enzymes of the cascade. Its active site(s) are contained within four approximately 60 amino acid long units, termed complement control protein repeats (CCPs), which are suspended above the cell surface on a 68 amino acid long serine/threonine (S/T)-rich cushion that derives from three exons. We previously proposed a molecular model of human **DAF**'s four CCPs in which certain amino acids were postulated to be recognition sites for the interaction between **DAF** and the C3 convertases. In the current study, we characterized **DAF** in five non-human primates: the great apes, gorilla and common chimpanzee, and the Old World monkeys: hamadryas baboon, Rhesus macaque, and patas monkey. Amino acid homology to human **DAF** was approximately 98% for the two great apes and 83% for the three Old World monkeys. The above cited putative

ligand interactive residues were found to be fully conserved in all of the non-human primates, although there were amino acid changes outside of these areas. In the chimpanzee, alternative splicing of the S/T region was found potentially to be the source of multiple protein isoforms in erythrocytes, whereas in the patas monkey, similar alternative splicing was observed but only one protein band was seen. Interestingly, a Rhesus macaque was found to exhibit a phenomenon paralleling the human Cromer Dr(a-) blood group, in which a 44-base pair deletion in CCP3 leads to a frameshift and early STOP codon.

L47 ANSWER 8 OF 10 MEDLINE on STN
2000463155. PubMed ID: 11012760. Structure/function studies of human decay-accelerating factor. Brodbeck W G; **Kuttner-Kondo L**; Mold C; Medof M E. (Department of Pathology, Case Western Reserve University, Cleveland, OH, USA.) Immunology, (2000 Sep) Vol. 101, No. 1, pp. 104-11. Journal code: 0374672. ISSN: 0019-2805. L-ISSN: 0019-2805. Report No.: NLM-PMC2327052. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The decay-accelerating factor (**DAF**) contains four complement control protein repeats (CCPs) with a single N-linked glycan positioned between CCPs 1 and 2. In previous studies we found that the classical pathway regulatory activity of **DAF** resides in CCPs 2 and 3 while its alternative pathway regulatory activity resides in CCPs 2, 3 and 4. Molecular modelling of the protein predicted that a positively charged surface area on CCPs 2 and 3 (including KKK125-127) and nearby exposed hydrophobic residues (L147F148) on CCP3 may function as ligand-binding sites. To assess the roles of the N-linked glycan and the above two sets of amino acids in the function of **DAF**, we mutated N61 to Q, KKK125-127 to TTT and L147F148 to SS. Following expression of the mutated cDNAs in Chinese hamster ovary cells, the glycosylphosphatidylinositol (GPI)-anchored mutant proteins were affinity purified and their functions were assessed. In initial assays, the proteins were incorporated into sheep and rabbit erythrocytes and the effects of the mutations on regulation of classical and alternative C3 convertase activity were quantified by measuring C3b deposition. Since **DAF** also functions on C5 convertases, comparative haemolytic assays of cells bearing each mutant protein were performed. Finally, to establish if spatial orientation between **DAF** and the convertases on the cell surface played any role in the observed effects, fluid-phase C3a generation assays were performed. All three assays gave equivalent results and showed that the N-linked glycan of **DAF** is not involved in its regulatory function; that L147F148 in a hydrophobic area of CCP3 is essential in both classical and alternative pathway C3 convertase regulation; and that KKK125-127 in the positively charged pocket between CCPs 2 and 3 is necessary for the regulatory activity of **DAF** on the alternative pathway C3 convertase but plays a lesser role in its activity on the classical pathway enzyme.

L47 ANSWER 9 OF 10 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2000:394961 Document No.: PREV200000394961. Characterization of the active site in decay-accelerating factor (**DAF**). **Kuttner-Kondo, Lisa** [Reprint author]; Mitchell, Lynne; Hourcade, Dennis; Medof, M. Edward [Reprint author]. Case Western Reserve Univ., Cleveland, OH, USA. Immunopharmacology, (August, 2000) Vol. 49, No. 1-2, pp. 64. print. Meeting Info.: XVIIIth International Complement Workshop. Salt Lake City, Utah, USA. July 23-27, 2000.
CODEN: IMMUDP. ISSN: 0162-3109. Language: English.

L47 ANSWER 10 OF 10 MEDLINE on STN
1997164204. PubMed ID: 9010927. Molecular modeling and mechanism of action of human decay-accelerating factor. **Kuttner-Kondo L**; Medof M E; Brodbeck W; Shoham M. (Institute of Pathology, Case Western Reserve

University, Cleveland, OH 44106-4935, USA.) Protein engineering, (1996 Dec) Vol. 9, No. 12, pp. 1143-9. Journal code: 8801484. ISSN: 0269-2139. L-ISSN: 0269-2139. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A model of the regulatory region of human decay accelerating factor (**DAF**) was built based on the known coordinates of a fragment of the structurally and functionally homologous serum protein, factor H. According to this model, the four short consensus repeats (SCRs) in **DAF** are arranged in a helical fashion. A positively charged surface area on SCRs 2 and 3, two of the three repeating units essential for function, is postulated to be the primary recognition site for the C3 convertases C4b2a and C3bBb. This area encompasses a cavity on SCR 2, as well as part of the groove on the SCR 2-SCR 3 interface. Two additional surface depressions are centered around the C-terminal disulfide bridges of SCRs 3 and 4. These are likely to provide additional ligand binding sites. Based on this model in conjunction with sequence homology to the Ba fragment of factor B, a mechanism of **DAF**'s accelerated convertase decay action is postulated.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	186.96	194.89

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-21.25	-21.25

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